Anticancer activity of botanical compounds in ancient fermented beverages (Review)

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Abstract. Humans around the globe probably discovered natural remedies against disease and cancer by trial and error over the millennia. Biomolecular archaeological analyses of ancient organics, especially plants dissolved or decocted as fermented beverages, have begun to reveal the preliterate histories of traditional pharmacopeias, which often date back thousands of years earlier than ancient textual, ethnohistorical, and ethnological evidence. In this new approach to drug discovery, two case studies from ancient Egypt and China illustrate how ancient medicines can be reconstructed from chemical and archaeological data and their active compounds delimited for testing their anticancer and other medicinal effects. Specifically, isoscopoletin from Artemisia argyi, artemisinin from Artemisia annua, and the latter’s more easily assimilated semi-synthetic derivative, artesunate, showed the greatest activity in vitro against lung and colon cancers. In vivo tests of these compounds previously unscreened against lung and pancreatic cancers are planned for the future.

1. Introduction

Ethnohistorical accounts and modern ethnological practices of peoples around the world provide a rich source of potential natural products (animal, plant, and mineral) for discovering lead molecular structures for new drugs. We have only to consider the alkaloid quinine, derived from the bark of South American trees and shrubs (Cinchona spp), which was recognized as effective against malarial fever by native Peruvians since at least the 17th c. (1). The compound was isolated in 1820, and it saved countless lives in the following century and a half. Similarly, references in ancient Mesopotamian, Egyptian, and Greek texts provided the impetus for the isolation and eventual modification of salicylic acid from willow tree bark (Salix spp.) in the 19th century; acetylsalicylic acid (aspirin) is today the most widely used pharmaceutcal palliative.

Another natural product, which has been extensively investigated by one of the co-authors (M. Christofidou-Solomidou), is flaxseed, derived from the flax plant (Linum usitatissimum). This annual herb, one of the founder plants of the Near Eastern ‘Neolithic Revolution’, became an important part of the ancient Egyptian pharmacopeia, and is still important in the traditional medicine of the region. The high percentage of ω-linolenic acid, an ω-3 fatty acid, and lignans in flaxseed have been shown to be protective against breast and colon cancer (2,3). More recently, flaxseed was shown to possess potent antioxidant and anti-inflammatory properties (4-6). Encouraging in vitro and in vivo findings have led to the initiation of several clinical trials using flaxseed and flax-derived lignans in the USA, Europe and China.

In North America, European explorers observed the native peoples steeping Canada yew needles (Taxus canadensis) to make a tea for treating arthritis (7). A National Cancer Institute study in 1967 showed that one compound in yew bark, paclitaxel, is a strong inhibitor of a host of cancers, especially ovarian and breast. Under the trademark TAXOL, this drug has since become the largest selling anticancer medicine in the world.

Many other successes of translating a traditional, natural remedy into an efficacious drug might be cited (8,9). For example, the development of the podophyllin class of anti-
cancer drugs grew out of native American observations that mayapple roots (Podophyllum peltatum) could mitigate skin cancer, and the anti-inflammatory and anticancer drugs triptolide and celastrol were a direct result of experimentation with the ‘thunder god vine’ (Trypterygium wilfordii Hook F.) of Traditional Chinese Medicine (TCM).

As these several parade examples show, plant exudates (including resins and nectar) and other structures (flowers, roots, leaves, etc.) have figured importantly in drug discovery. Yet, it has been estimated that only about 5,000 plant species (1.5-2%) out a total of 250,000-300,000 world-wide have been exhaustively studied for possible medical benefits (10). Overwhelmingly, their use in traditional medicine was the main criterion for their selection (11). This approach makes good sense, since it is a daunting task to construct large libraries of de novo synthetic compounds and test them for their medicinal effects. Nature has already carried out combinatorial chemistry on a vast scale to produce compounds, particularly secondary metabolites, which serve to ward off disease and noxious organisms, to prevent premature death (e.g., by cancer), and to promote growth and other physiological functions (12).

When the abundant productivity of nature is coupled with human observation and experimentation by trial and error over hundred of thousands if not million of years, stretching back into the Palaeolithic 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 maladies of all kinds that resulted in infant death and short life spans, their only recourse was to ‘experiment’ with the plants, other animals, minerals, and microorganisms. Even if the latter were 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 thousands of years. On the other hand, superstitions, misguided religious injunctions, or unfounded psychological notions might creep into a tradition over time (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 Revolutions 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 (13). 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.

Ancient textual, ethnological, and ethnohistorical pharmacological approaches provide important means to discover the medical ‘database’ of our ancestors. However, with the advent of biomolecular archaeology over the past 20 years, an independent method is now available, which avoids the ambiguities and accretions of later tradition embedded in written texts and oral accounts. By analyzing contemporaneous organic residues inside ancient containers, key natural products and organic compounds of potential medicinal value can be directly detected. Several case studies are presented to illustrate this potentially very effective approach, along with follow-up testing of important medicinal compounds to date.

2. Ancient Egyptian herbal wine, ca. 3150 B.C.

Fermented beverages, made from sweet fruits, honey and saccharified cereals, were likely discovered and utilized by humans at a very early date (14). All animals - from the fruit fly to the elephant - derive a significant amount of their energy from sugar resources. Alcohol from a fermenting natural product leads animals to sugar by putting up pungent plumes, besides providing its own metabolic resource (15). Indeed, based on ancient hominid dentitions and the diet of our nearest genetic relative - the chimpanzee - plants and fruits probably accounted for some 75-90% of ancient humans’ food intake. In the warm tropical climate of sub-Saharan Africa where the species emerged, these high-sugar resources can achieve alcoholic contents of 5% or more by natural fermentation.

Alcoholic beverages conferred many advantages to the human species when consumed in moderation. It was the universal drug up until the advent of modern medicine, since its health benefits were obvious - alcohol relieved pain, stopped infection, and killed microorganisms and parasites in tainted water. Alcoholic beverages also served as social ‘lubricators’, facilitating social communication and easing the difficulties of everyday life. As a mind-altering substance, it entered into religious practice. But from a medical standpoint, the alcohol in fermented beverages enabled plant compounds, whether from fruits, tree resins, flower nectars, roots, herbs or spices, to be taken into solution (16).

‘Medicinal wines’ and external salves, with anesthetic, antimicrobial, and psychotropic properties are recorded in ancient Egyptian medical forays can be pushed back into prehistoric times.

In a recent study (17), a residue sample from inside a jar (Fig. 1) belonging to one of the first rulers of ancient Egypt, Scorpion I of Dynasty 0, was analyzed. The jar was one of some 700, stacked high in three chambers, of an exceptionally rich tomb (denoted U-j) at the site of Abydos (18) (Fig. 1).

Analysis by a variety of techniques [including Liquid Chromatography Tandem Mass Spectrometry and Headspace Solid Phase Microextraction (SPME) and Thermal Desorption (TD) Gas Chromatography-Mass Spectrometry (GC-MS)] showed that this jar and others had contained a grape wine. The wine, however, was not a pure varietal, which is the goal of many winemakers today. In addition to whole grapes and figs, a pine and/or terebinth tree resin had been added to the wine. Eight terpenoid compounds - linalool, camphor, borneol, L-menthol, α-terpineol, carvone, thymol, and geranyl acetone - provided further evidence that a range of herbs of Levantine origin, where the wine had been made and then exported to Egypt, were also added.

These herbs could be tentatively identified by a thorough search of the chemical literature using bioinformatics search engines (see Methodological approach, below). Species of
pine resin and figs were also added. Ht. of sherd 33.5 cm. Photograph from the tomb (U-j) of Scorpion I at Abydos (Egypt), ca. 3150 B.C. (Hartung 2001: cat. no.156, pls. 58: and 94:156). The residue, forming a circle around the vessel's interior, is slanted off from the horizontal, because the jar with its liquid was tilted in antiquity. Analyses showed that herbs including balm, coriander, mint, sage and many more were steeped in the wine, to which the residue, the accumulation of ancient organic materials from the upper surface of the grape wine that once filled the inside of jar no. 50 from the tomb (U-j) of Scorpion I at Abydos (Egypt), ca. 3150 B.C. (Hartung 2001: cat. no.156, pls. 58: and 94:156). The residue, forming a circle around the vessel's interior, is slanted off from the horizontal, because the jar with its liquid was tilted in antiquity. Analyses showed that herbs including balm, coriander, mint, sage and many more were steeped in the wine, to which pine resin and figs were also added. Ht. of sherd 33.5 cm. Photograph courtesy of German Archaeological Institute in Cairo.

Figure 1. A yellowish residue, the accumulation of ancient organic materials from the upper surface of the grape wine that once filled the inside of jar no. 50 from the tomb (U-j) of Scorpion I at Abydos (Egypt), ca. 3150 B.C. (Hartung 2001: cat. no.156, pls. 58: and 94:156). The residue, forming a circle around the vessel's interior, is slanted off from the horizontal, because the jar with its liquid was tilted in antiquity. Analyses showed that herbs including balm, coriander, mint, sage and many more were steeped in the wine, to which pine resin and figs were also added. Ht. of sherd 33.5 cm. Photograph courtesy of German Archaeological Institute in Cairo.

ten botanical genera accounted for the most compounds - savory (Satureja), wormwood/mugwort (Artemisia), tansy (Tanacetum), balm (Melissa), senna (Cassia), coriander (Coriandrum), germander (Teucrium), mint (Mentha), sage (Salvia), and thyme (Thymus/Thymbra). They were thus the most likely additives used individually or in combination.

At first, we were surprised to discover that the Scorpion I wine had been 'adulterated' with so many additives. A tree resin was the least surprising, since our analyses of numerous ancient residues from throughout the Middle East and Mediterranean over millennia has shown that a popular, widespread practice in antiquity was to resinate wine. Besides covering up off-tastes and aromas, tree resins contain anti-oxidant compounds which help to preserve the wine. Resinated wines were still being made in the Middle Ages, according to the extensive agricultural and medical compilations based on classical writings, collectively known as the Geoponica (19).

The finding of herbal additives in the Scorpion I wine, however, made us suspect that the Levantine winemakers and their Egyptian clients might well have had a more far-reaching purpose in preparing and consuming such mixed beverages. Egypt has one of the most ancient and detailed materia medica in the world, based on archaeobotanical findings and literary traditions (20,21). Papyri, dating back to the mid-12th Dynasty, ca. 1850 B.C., show that 'medicinal wines' were very important to the Egyptian 'physician' (swnw, the hieroglyphic word, is attested as early as Dynasty 3, ca. 2650 B.C.).

More than a thousand prescriptions are recorded in the ancient Egyptian medical papyri. Most numerous are those that list alcoholic beverages - wine and beer - as dispensing agents, and in which tree resins (terebinth, pine, frankincense, myrrh, fir, etc.) and numerous herbs (bryony, coriander, cumin, mandrake, dill, aloe, wormwood, etc.) are added ingredients. The plants and their exudates were macerated, mixed together, and steeped in these beverages; they were administered for specific ailments. Traditional Egyptian medicine today still uses many of the same formulations. Based on the continuity of Egyptian medicine over thousands of years, it is reasonable to project it further back into the past, to account for the biomolecular and archaeobotanical evidence from the Scorpion I wine jars.

After establishing the possible natural product additives to the Scorpion I wine, our next step was to search the available scientific literature for any active medicinal compounds reported for these ingredients. Our specific focus has been anticancer compounds, since our collaborative program at the University of Pennsylvania Medical Center is in this area. Because most of the numerous plant terms and diseases in the ancient Egyptian prescriptions cannot be translated or identified as yet, we cannot be certain which herb or other plant material is specifically associated with a given cancer. However, Egyptian morticians and physicians, who mumified the dead, would have had detailed anatomical knowledge of ancient internal and external cancers. Specific remedies were likely developed to treat such cancers. On this assumption and according to our in vitro screening of lung and colon cancers, the most promising anticancer compounds in the Scorpion I wine are luteolin found in (sage) and ursolic acid (a triterpenoid in thyme and other herbs). Ursolic acid causes cancer cell death under hypoxic conditions, which may warrant further investigation (see below).

3. Ancient Chinese herbal wine, ca. 1050 B.C.

To date, our earliest evidence of an alcoholic beverage from anywhere in the world, which might have been used medicinally, is from the Neolithic site of Jiahu in the Yellow River Valley of China, dating back to ca. 7,000 B.C. (22). Biomolecular archaeological analyses of pottery jars which contained the beverage showed that the ancient beverage had been formulated from rice, honey, a Chinese grape species, and hawthorn tree fruit. This finding is obviously of great interest 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.) - 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., 23,24). Since we have not yet analyzed the extracted residues from the Jiahu jars by SPM or TD GC-MS, it is not known whether any herbs or spices, which might have anticancer or other medicinal
properties, were added to the ancient mixed beverage. Other than several well-known and studied anti-oxidant compounds from grape (e.g., resveratrol) and hawthorn fruit, our survey of the literature did not reveal any additional active anticancer compounds to be screened.

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 wine in the oracle bone inscriptions. Officials in the Shang palace administration were charged with making the beverages, which the king inspected. Our TD GC-MS analysis of liquid, amazingly still contained inside a lidded bronze jar (Fig. 2) from the Changzikou Tomb in Henan Province (ca. 1050 B.C., contemporaneous with the oracle bone inscriptions), illustrates what information can be gleaned via biomolecular archaeology (22). The tight lid on the jar accounts for the liquid having not evaporated: it had corroded to the neck, hermetically sealing off the jar's contents until the tomb was excavated thousands of years later.

The analysis revealed that two aromatic compounds - camphor and α-cedrene - were present in the ancient beverage, in addition to benzaldehyde, acetic acid, and short-chain alcohols characteristic of rice and grape wines. Stable 13C and 15N isotope measurements identified the beverage as rice-based. 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 *Artemisia annua* and/or *A. argyi* in the wormwood/mugwort genus [N.B.: Shin (25) now reports α-cedrene to be present in *A. annua* (26)]. If an *Artemisia* 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 (Fig. 2).

Of the possible ingredients and additives identified in the Changzikou wine, the two species of *Artemisia* stood out because of their long-standing importance in TCM up to the present day. Both *A. annua* (wormwood) and *A. argyi* (mugwort), usually equated in TCM with *Ait Ye* respectively (27), were cited in the earliest Chinese medical prescriptions, the Mawangdui tomb texts dating to 168 B.C. (28). There, *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. *Ait 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' by Li Shizen, published in 1596 A.D., attests to the long medicinal use of *Artemisia* herbs in TCM when it cites Ge Hong's (284-364 A.D.) 'Handbook of Prescriptions for Emergency Treatment.' As for the highly developed ancient Egyptian pharmacopeia, it is likely that ancient Chinese physicians had detailed anatomical knowledge of the human body, including many different kinds of cancer, 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 (below). Its semi-synthetic analogue, artemisunate, was even more effective against colon cancer (29) and many others, including Kaposi's sarcoma (30), uveal melanoma (31,32), hepatitis C (33) and ascitic liver tumor (34), ovarian cancer (35), pancreatic cancer (36), neuroblastoma (37), and myeloid leukemia (38). 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 (39).

Because of the importance of *A. annua* in TCM, it was chosen during the Vietnam War as a prospective herb for testing against malaria (32,40). The anticancer properties of the herb's principal active compound, artemisinin, were subsequently discovered, and still remain to be fully elucidated (41-53). Efferth and colleagues (54) 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.

Another active compound which showed promise against cancers in our in vitro screening (below) - isoscopoletin, a coumarin flavone - has thus far been obtained only from A. argyi in this genus. Other researchers (55) have documented this compound's cytotoxicity against leukemia cells, likely by inhibiting the activity of farnesyl protein transferase (FTPase). Both A. argyi and annua are sources of borneol, a monoterpene, which also exhibited some anticancer activity in our studies.

4. Methodological approach

Because of the novelty of using biomolecular archaeology to target potential compounds for anticancer testing, some additional explanation of its prospects and limitations is helpful.

Our ability to identify compounds in an ancient residue is only as good as the instrumentation available, which is constantly improving. Moreover, how well the residue was preserved, which depends on its archaeological context and environmental factors, is crucial in detecting any intact organics or their degradation products.

Once the compounds in the ancient residue have been established, bioinformatics tools - SciFinder Scholar, the Kirk-Othmer Encyclopedia of Chemical Technology, Dr Duke's Phytochemical and Ethnobotanical Databases, the chemical database of the Amber Research Laboratory of Vassar College, etc. (56-59) - are employed to discover the original natural products. Marker or fingerprint compounds, which are characteristic of specific plants, are most important. Sometimes a single compound, such as tartaric acid which uniquely points to the Eurasian grape (Vitis vinifera) in the Middle East (17), will be found. Other samples may yield many compounds, none of which is sufficient by itself to isolate the natural product, but together may provide the probable plant(s) according to Occam’s razor or rule, viz., the simplest, most straightforward explanation is the right one.

Our interpretation of the biomolecular archaeological data greatly depends on which natural products have thus far been analyzed and published. Even with the powerful bioinformatics methods currently available, only as good as the instrumentation available, which is constantly improving.

5. In vitro studies of active compounds: materials and methods

Based on the biomolecular archaeological results for the ancient Egyptian and Chinese fermented beverages, coupled with our extensive literature search, the following potentially active, high-purity (>97%) compounds were tested: i) luteolin (Sigma L9283), present in Salvia; ii) ursolic acid (Fluka 89797), present in Thymus; iii) artemisinin (Aldrich 361593), present in A. annua; iv) artesunate (AvanChem Scientific 1562 and Sigma A3731), a derivative of artemisinin; v) borneol (Fluka 15599), present in A. argyi; vi) bornyl acetate (Sigma W21590-2), present in A. argyi; vii) isoscopoletin (ChromaDex ASB-00009570-010), present in A. argyi; and viii) scopoletin (Sigma S-2500), present in A. argyi. The staining agent, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), was obtained from Promega (G5430).

For the in vitro tests in Wafik El-Deiry’s laboratory, HCT116 colon adenocarcinoma cell lines, expressing a firefly luciferase p53 reporter PG13-luc (62), which was a comparison for any cytotoxic effects. The luciferase activity was imaged by a Xenogen IVIS imaging system.

Cell proliferation tests were then performed in M. Christofidou-Solomidou’s laboratory that were focused only on artemisinin and artesunate, which had shown greatest promise in the p53 induction experiments. Murine Lewis lung carcinoma (LLC) cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM) containing 10% heat-inactivated fetal bovine serum (FBS) at 37°C in a humidified atmosphere of 5% CO2. LLC cells were added to a 96-well plate at a density of 5,000 cells/well and allowed to adhere
overnight. Cells were first treated with various concentrations of artemisinin and artesunate or the solvent vehicle dimethyl sulfoxide (DMSO) and incubated for 24, 48 and 72 h, following which they were assessed for their proliferation using a routine MTT assay (63). Briefly, 100 μl of 0.5 mg/ml MTT solution was added to each well, the cells incubated for 2 h at 37˚C, and the optical density measured using a microplate reader (Bio-Rad 680). All conditions were run in triplicate. Two series of experiments were carried out: i) concentrations of 25, 50, 100, 200, 400, 500 and 800 μM of artemisinin and artesunate were added only once to the cells, at the start of the experiment, and ii) lower doses of artesunate (1, 2, 4, 8, 25, 50, 100 and 200 μM) were added to the cells each day of the experiment for 1-, 2-, or 3-day periods.

6. Discussion and conclusions

Biomolecular archaeological evidence, which is increasingly retrievable from ancient containers using microchemical techniques, points to a long history of medicinal and anti-cancer remedies that were tried, tested, and sometimes lost throughout the millennia since the human species emerged in Africa and spread out across the planet starting around 100,000 years ago. Our ancestors might well have discovered empirically some of the most potent and medicinally effective plants in their environments, especially in periods of experimentation as epitomized by the Neolithic Revolutions beginning 10,000 years ago, after the end of the last Ice Age. Plants, including herbs, tree resins, and other organics were ideally dissolved in and dispensed by ancient fermented beverages, such as wine and beer (14).

Two case studies, one detailing a biomolecular archaeological study of the earliest grape wine yet found in ancient Egypt (ca. 3150 B.C.) and the other describing the chemical findings of a liquid recovered inside a Shang Dynasty stoppered bronze vessel (ca. 1050 B.C.), show how the new field of bioarchaeological oncology can significantly broaden and contribute to traditional ethnopharmacological approaches. The latter are necessarily limited to traditional practices, such as TCM, or are based on relatively recent oral and written traditions, which can be variously interpreted.

The biomolecular archaeological evidence is derived directly from residues of ancient vessels, sometimes thousands of years old, and is contemporaneous with its medicinal use. Although one cannot always be certain that a specific organic additive to an alcoholic beverage was originally intended as a medicinal or anticancer agent, this can be reasonably inferred, especially if there exists a strong later textual tradition which can then be projected back into the past. Ancient Egypt and China are prime examples of cultures in which a long pharmacological history provides excellent supporting evidence. In some instances, the same plants which have been identified by biomolecular archaeological analyses...
The protein p53 serves as a genome guardian and plays a fundamental role in tumorigenesis, tumor progression, and therapeutic response of tumors (64). It functions mainly as a transcription factor by binding to specific DNA sequences and by transactivating or repressing a large and ever-increasing group of target genes. The latter in turn regulate the pathways of cell-cycle arrest, apoptosis and DNA repair, thereby maintaining a dynamic equilibrium between cell growth, arrest and death under stressful conditions, including DNA damage, hypoxia. A strategy in anticancer therapy is to counteract this property of tumor cells. It may be hypothesized that the anticancer potency of ursolic acid is related to mechanisms operating under hypoxia (Fig. 5).

As more and more plants from around the world are chemically analyzed, large gaps in databases will be filled in, and as microchemical methods improve, the prospects for biomolecular archaeological oncology will grow. We are just at the beginning of ‘Digging for Drug Discovery,’ as this new multidisciplinary approach to ancient ethnopharmacology expands and matures.

(e.g., A. annua and A. argyi) are specifically mentioned in their earliest pharmacopeias. By taking advantage of careful observations by our human ancestors, albeit by simple trial and error, discovering lead structures for combinatorial exploration can be streamlined and made more efficient. Based on these results, we propose in vivo and clinical studies of one derivative compound from A. annua in particular: artesunate. As already known from in vivo mouse studies of other cancers, we plan to test this compound for its clinical efficacy against lung and pancreatic cancer. To date, the effectiveness of artesunate against these specific cancers has not been determined.
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