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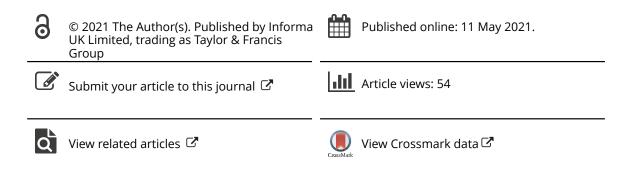
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# A Response to Léa Drieu et al., 2020, "Is It Possible to Identify Ancient Wine Production Using Biomolecular Approaches?" (*STAR: Science & Technology of Archaeological Research*, DOI:10.1080/20548923.2020.1738728)

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#### ABSTRACT

Comparable to Drieu et al.'s viewpoint, we argue that it is possible to identify ancient Eurasian grape wine by current biomolecular methods, but only in conjunction with the relevant archaeological, archaeobotanical, and other natural and social scientific data. Additionally, we advocate an inductive-deductive working hypothesis model, which is appropriate for the "historical science" of archaeology. We focus on two key deficiencies of Drieu et al.'s argumentation: (1) the assumption that Guasch-Jané et al. (2004) extracted their ancient samples with potassium hydroxide before testing for tartaric acid/tartrate, and (2) the supposition that 5000-year-old yeast DNA would not be preserved in the hot climate of Egypt but rather represents modern contamination.

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Drieu et al. recently published a review article ("Is it possible to identify ancient wine production using biomolecular approaches?") in this journal. In their article, they address the question, "How reliable are methods for the extraction and detection of tartaric acid in archaeological samples?" (17) by comparing "two of the most common extraction methods" using modern wine samples and pure synthetic tartaric acid. Drieu et al. wrote,

We have shown that the method described as "alkaline fusion" and subsequent extraction with ethyl acetate (Guasch-Jané et al. 2004; Pecci et al. 2013) was highly inefficient (less than 0.1% yield for pure tartaric acid standard), due to the low solubility of tartaric acid in ethyl acetate.

We would point out that the specific alkaline fusion protocol used by Drieu et al. apparently originated from Pecci et al. (2013) and was not used by Guasch-Jané et al. (2004, 2006) for the extraction and analysis of tartaric acid. The alkaline fusion used by Guasch-Jané et al. was specifically designed to target syringic acid released from the flavylium structure of malvidin-3-glucoside in the aged (polymerized)

pigment. To analyse for tartaric acid, they used 0.1% formic acid in water/methanol (80:20 vol/vol) in their extraction of five ancient samples, four of which were positive for tartaric acid/tartrate, viz., BM1, BM2, CM1, and CM2 (Guasch-Jané et al. 2004, 1675, figs. 1A and 2). Subsequently, only one of these ancient samples, CM1, went through a second extraction by alkaline fusion with ethyl acetate in order to test for syringic acid (Guasch-Jané et al. 2004, 1676-1677). If potassium hydroxide had been part of the tartaric acid/tartrate extraction, it would certainly precipitate out insoluble salts, which would explain the <0.1% recovery yield using a pure tartaric acid standard by Drieu et al. It is also important to point out that the Guasch-Jané et al. extractions were performed on visible residues (~2 mg) deposited inside the jars (e.g. dry deposit of dark brown colour, thin encrustations on the inside of pottery jars) that were scraped out rather than extracting the ancient pottery sherds per se.

We would further emphasize that to "critically evaluate the diverse range of methodological approaches" as posed by Drieu et al. (16, abstract),

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more than two extraction methods should be carefully examined. Moreover, if such a comparison is carried out, then additional factors than those considered by Drieu et al. need to be addressed. For example, there is an important linkage between the extraction and the detection methods. Thus, Guasch-Jané et al.'s extraction solvent is tailored to the mobile phases used in their successfully detecting tartaric acid/tartrate by liquid chromatography with tandem mass spectrometry (LC-MS/MS). By contrast, gas chromatography-mass spectrometry (GC-MS), which is the preferred method of Garnier and Valamoti (2016) and Drieu et al., need to follow a different extraction and detection route, especially since common derivatization agents cannot be used in conjunction with water that will cause hydrolysis of the targeted compounds, thereby limiting what can be tested for by this technique unless precautions are taken. Consequently, care must be taken when trying to adapt extraction techniques intended for LC-MS/ MS to another analytical platform such as GC-MS.

We have experimented with many different extraction procedures over the past two decades in preparing ancient pottery samples for analysis by LC-MS/MS and liquid chromatography high-resolution Orbitrap mass spectrometry (LC-HRMS), which are currently the most sensitive and accurate chemical techniques for the detection of tartaric acid/tartrate. In brief, accurate mass measurements from the Orbitrap mass analyzer (<3 ppm relative mass error from the theoretical mass-to-charge ratio [m/z]) enable the unambiguous assignment of molecular formulas. Furthermore, extracted ion chromatograms from LC-HRMS are generated using very narrow mass windows (as a result of both high mass resolution and mass accuracy), which significantly improves the signal-to-noise ratio and usually completely removes interferences for more accurate quantification (McGovern et al. 2013b, 2017). For LC-MS/MS, triple quadrupole instruments provide the highest sensitivity in multiple reaction monitoring (MRM) mode and the limit of detection (with a signal-to-noise ratio of 3) was previously determined to be  $0.05 \mu g/L$  for tartaric acid (Guasch-Jané et al. 2004).

Our group's preferred extraction method at present is to add a 1–2.8% ammonium hydroxide solution in water/methanol (80:20, vol/vol) to a 50–200 mg powdered sample (McGovern, Mirzoian, and Hall 2009, 2013a, 2013b, 2017). Depending on the resinous character of a sample, several millilitres of methylene chloride might be added for dissolving the resin. After stirring overnight and ultrasonicating for 1 h, the mixtures are centrifuged for at least 10 min at 4400 rpm to clarify the layers and to cause any remaining materials and emulsions to precipitate. The upper basic aqueous layer is then removed, reduced in volume by evaporating off the methanol and/or reducing the water content, filtered through a  $0.45 \,\mu\text{m}$  membrane, transferred to a high-performance liquid chromatographic (HPLC) vial, and analysed.

Additional concentration and purification can also be achieved by solid-phase extraction (SPE). Currently, we pass our ammonium hydroxide sample extracts through a reverse-phase SPE column with anion exchange properties (McGovern et al. 2013b, Supporting Information, p. 2). After the column is conditioned with methanol and ultrapure water, the extract is loaded onto it and rinsed with 5% ammonia in water and then methanol. Tartaric acid and other organic acids are eluted from the column with 5% formic acid in methanol. This eluate is dried, re-suspended in 2.8% ammonia in water, and transferred to an HPLC vial for analysis.

The principal advantage of using an alkali base, such as ammonium hydroxide, is that we have found it to be very effective in releasing salts of tartaric and other acids from an ancient pottery fabric, which is the most common material for wine containers in antiquity, and putting them into solution as anions. Specifically, ammonium tartrate has a relativity high solubility in water (638.1 g/L at 30 °C) when compared with the nearly insoluble potassium bitartrate, which forms naturally in wine, and can also precipitate out as calcium tartrate in calcareous geological regimes by the interchange of potassium with calcium cations (Waterhouse et al. 2016). We also use elevated temperatures in our extraction process, which further enhances the recovery of acidic anions.

It also needs to be stressed that we follow the identical extraction and analytical protocols for soil samples from the same or comparable archaeological contexts as those of the vessels being analysed. The direct comparison of the contents of the key grape organic acids enables possible contamination by microbes, ground-water percolation, and human handling to be monitored and controlled for. Drieu et al. advocate this approach, but rely principally on cooking pots, tiles, and "sediments" whose contexts are not specified. Much higher ratios of sherd organic acid contents to those of the soils, together with high absolute amounts (generally exceeding the hypothetical cut-off point of >0.3  $\mu$ g/g of pottery advocated by Drieu et al.) are to be preferred in establishing "true positives."

Based upon such considerations outlined above and further below, we conclude that the conclusion reached by Drieu et al. (25) that "Tartaric acid can be reliably extracted from archaeological artefacts but **only** [emphasis added] using the method of Garnier and Valamoti (2016)" is not accurate. Our extraction and analytical procedures are also acceptable.

Drieu et al. question another of our findings involving another biomolecular technique – DNA analysis - when they write that "the central conclusion of ancient yeast DNA does not stand up to scrutiny" (24). They are referring to our analysis of ancient DNA from *Saccharomyces cerevisiae*, the wine yeast, that we reported for residues inside the probable wine jars of the so-called Scorpion I tomb (U-j) at Abydos in Egypt, dated to ca. 3150 B.C. and imported into Egypt from the southern Levant (Cavalieri et al. 2003). Their principal arguments are (1) that Egypt's climate was too hot for 5000-year-old intact DNA to have been preserved, and (2) that the putative ancient yeast is more likely to be a modern contaminant yeast strain, commonly found in laboratories.

On the contrary, the analysed residues from the interiors of the jars, whose mouths had initially been sealed, were well protected from the sun in an extremely low-humidity environment of the Western Saharan Desert of Upper Egypt, which has likely persisted there for the past 5000 years. In short, the jars probably remained relatively cool and dry for millennia, which in turn helped to preserve the fragments of yeast DNA together with other organic material in the jars (viz., dried figs and raisins).

It should also be noted that Drieu et al. do not include a specific reference nor details of their calculation, which evidently requires knowing the sample depth, which is uncertain but >0.5 m. Since a depth measurement was not provided in our Response, it is uncertain how  $\lambda = 0.3011$  was determined and what significance it has for the preservation of ancient DNA. Moreover, the rate of depurination depends significantly on the sequence itself (Ran et al. 2014).

Modern contamination can be ruled out, because *S. cerevisiae* is not airborne, is rare in nature, and does not live on human skin, making the probability very low that the archaeologists or the geneticists contaminated the samples. This yeast has never been described for desert environments.

In addition, Drieu et al. (24) incorrectly state that *S. cerevisiae* strain 288C is a common laboratory microorganism based on an article by Mortimer and Johnston (1986). Robert Mortimer, who was a co-author on our Scorpion I yeast paper, meant that 288 and related yeast strains are commonly used in DNA research (35). That does **not** mean, however, that they persist in a sterilized laboratory and could have possibly contaminated the Scorpion I samples. Polyphenolic compounds in the Eurasian grape also have strong antioxidant properties and, because they are well preserved according to Drieu et al. (25), might well have provided additional protection against chemical degradation of DNA (cf. Xia et al. 2010).

The published results are further assured by the analyses having been independently carried out in sterilized laboratories at Harvard and the University of Florence using the most exacting methodology available at the time. The four nucleotide mismatches between the modern wine yeast (*Saccharomyces cerevisiae*) and the ancient yeast in the ribosomal region of chromosome 12 are best explained as deriving from the ancient grape/wine, since this region performs a critical function in translation and is functionally and structurally conserved evolutionarily.

We have other substantive issues with the Drieu et al. article that, in our opinion, have resulted in an overly sceptical view of past research on ancient wine and alternative methodologies and approaches. These include the corroborative value of malic, citric, and succinic acids for identifying a fermented Eurasian grape wine, and the use of multiple chemical techniques in fully characterizing adjunct and herbal ingredients in grape wine. We would also recommend that full archaeological and archaeobotanical details of analysed samples be provided, to properly evaluate the chemical data. Additional desiderata include how best to establish statistically significant sample sizes, effectively employing bioinformatics searches for discovering natural products that account for the chemical data, and the correct application of the term "false positive." We have focused here on the two most critical shortcomings of the paper, viz., the extraction method for tartaric acid/tartrate and the preservation and identification of ancient yeast DNA. We hope to address these and other reservations in a separate review article on ancient vinicultural research.

Drieu et al. (25) conclude their article by stating that "With the current state of knowledge, it is not possible to identify wine production using **only** [emphasis added] biomolecular approaches." If this statement means that the chemical data must be integrated into a holistic, interdisciplinary scientific approach, as advocated elsewhere in the article, then we agree. If instead, the statement implies that current chemical methods are insufficient as supporting evidence for the presence of ancient Eurasian grape wine, then we would disagree.

If ancient grape/wine is to be determined **only** by chemical techniques, such as metabolomics or "next generation" DNA sequencing, then absolute certainty will always remain elusive, because biomolecular archaeology is a "historical science" that depends on constrained and degraded archaeological remains (McGovern and Hall 2016). Chemistry, archaeology, and ancillary historical and social sciences need to work in concert in developing working hypotheses, such as that for "ancient wine production," and then test them by deducing plausible inferences that either support or nullify a hypothesis. Gradually, as tests are verified by multiple chemical techniques and other approaches, confidence in a hypothesis grows for specific sites, ecozones, and time periods. When corroborative evidence is not forthcoming, then further testing is needed before the hypothesis is accepted, partially modified, or abandoned.

Our perspective on the prospects of identifying ancient grape wine is more positive than that of Drieu et al. As a result of the biomolecular archaeological investigations already carried out on ancient viniculture, we now know much more about the historical course of an important ancient technology and how it functioned culturally at many different levels of abstraction - from the practical (production) to the mundane ("social lubrication") to a very complex human activity (commensality, religion, trade, medicine, etc.) (McGovern 2019a and 2019b). Working hypotheses of ancient vinicultural have largely stood the test of time, with modifications, because they were originally based on multidisciplinary lines of evidence, as well as a methodological, theoretical, and experimental approach appropriate to any historical science.

We do share Drieu et al.'s optimism that the continued development of chemical techniques will lead to better results and more assured conclusions (as reviewed and detailed in the updated Afterword of McGovern 2019a, especially "Deciphering the Wine Cultures of Past and Present").

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This response to the Drieu et al. article would not have been possible without very fruitful discussions with and information provided by a legion of fellow scientists, archaeologists, colleagues, and wine lovers worldwide. They are amply recognized for their many contributions in the cited references. We particularly thank Armen Mirzoian of the Scientific Services Division of the Alcohol and Tobacco Tax and Trade Bureau (U.S.A.), Régis Gougeon of the Institut Universitaire de la Vigne et du Vin-Jules Guyot, Université de Bourgogne, Dijon (France), Philippe Schmitt-Kopplin of the Analytical Biogeochemistry unit, Helmholtz Zentrum, Munich (Germany), and Ulrich Hartung of the German Institute of Archaeology in Cairo (Egypt). It is hard to imagine a better topic than ancient grape/wine, which brings together the exactitude of the sciences and the cultural dimensions of history and the humanities through time and around the world.

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