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**PAPER**

**TOXICOLOGY**

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# Quantification of Morphine, Codeine, and Thebaine in Home-Brewed Poppy Seed Tea by LC-MS/MS

**ABSTRACT:** Recently, medical examiners reported two cases of a 21-year-old male and 24-year-old male with high amounts of morphine in their blood at autopsy. It was suspected that the decedents ingested lethal amounts of morphine from home-brewed poppy seed tea. No studies to date have investigated opium alkaloid content extracted from poppy seeds by home-brewing methods. Various poppy seed products were purchased from online sources and extracted with four home-brewing methods representative of recipes found on drug user forums. Morphine, codeine, and thebaine were quantified in the tea extracts by liquid chromatography-tandem mass spectrometry using a validated analytical method. Morphine, codeine, and thebaine concentrations from seeds were <1–2788 mg/kg, <1–247.6 mg/kg, and <1–124 mg/kg, respectively. Alkaloid yield varied between extractions, but regardless of extraction conditions, lethal amounts of morphine can be rinsed from poppy seed coats by home-brewing methods.

**KEYWORDS:** forensic science, forensic toxicology, morphine, opium, poppy seed tea, liquid chromatography-tandem mass spectrometry

Morphine and codeine are two naturally occurring opiates in the opium poppy (*Papaver somniferum*) and are therapeutically used for pain management (1). Morphine, codeine, and their derivatives have agonistic effects on μ-, K-, and δ-opioid receptors in the body's pain pathway (2). A consequence of long-term opiate use is the rapid development of tolerance to analgesic effects while tolerance to undesirable side effects, such as respiratory depression, develops more slowly (3). The effective dose can increase rapidly for long-term opiate users, but the lethal dose does not typically increase in the same manner, limiting how much a prescription can be increased (3).

*In vivo* studies in animal models have estimated lethal doses for both morphine and codeine in 50% of the sample populations (LD50) (4,5). These data are difficult to estimate for humans particularly due to differences in tolerance. However, lethal doses for morphine and codeine in humans can be inferred from overdose case reports where these drugs are implicated (6–8).

Prescription forgery and the black market are common ways of obtaining licit narcotic analgesics through illicit means (9). In some cases, addicts have also tried novel, alternative methods of managing their pain and withdrawal symptoms. The level of information that is shared online contributes to the facilitation of drug abuse practices such as extracting opium alkaloids by brewing poppy seed tea (10). However, this practice can have fatal consequences.

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Morphine, codeine, and thebaine are found in the opium poppy latex (11,12). This latex is harvested by growers who make cuts in the pods before the pods ripen. The latex seeps out of these cuts and is collected as crude opium when it dries. Opium alkaloids are not found in the seeds of the opium poppy but are transferred onto the seed coats through this latex during the harvesting process (12). Both method of harvest and geographic origin can affect the morphine, codeine, and thebaine content on poppy seed coats (13). In addition, unwashed, or unprocessed, poppy seeds have a higher alkaloid content on their coats than washed poppy seeds. This makes unwashed poppy seeds desirable for drug users seeking to extract morphine and codeine from the seed coats. Unwashed poppy seeds can be purchased in bulk online from both domestic and international sources with no current legal repercussions or regulations.

This study stems from two recent morphine fatalities where poppy seed tea use was suspected. Previous studies have investigated morphine and codeine concentrations in biological specimens following controlled poppy seed administration (14–16). However, there is no peer-reviewed literature to date on extracting morphine, codeine, and thebaine from poppy seed coats in home-brewed poppy seed tea. Previous studies that did rinse opium alkaloids from poppy seed coats did so with laboratory chemicals for analytical extraction purposes in determining alkaloid content (12,14).

The goal of the present study was to determine whether lethal amounts of morphine can be extracted from poppy seed coats by home-brewing methods. Codeine concentrations were investigated because codeine is another opium alkaloid with analgesic properties, and codeine and morphine can have compounding effects when both drugs are taken simultaneously. Thebaine concentrations were investigated because thebaine's presence is relevant in sourcing morphine consumed by poppy tea users, although thebaine is not a narcotic analgesic nor is it addictive itself (17).

## Case Reports

### *Case 1*

A 24-year-old white male died from morphine intoxication with aspiration pneumonitis. The decedent's blood contained 0.25 mg/L morphine and 0.012 mg/L codeine at autopsy. The medical examiner also noted a trace amount of thebaine in the decedent's blood ruling out possible heroin intoxication. Neither illicit nor pharmaceutical sources of morphine were found at the scene. It is suspected that the decedent ingested a lethal amount of morphine from home-brewed poppy seed tea. A 5-lb bag of commercially obtained poppy seeds was located by the decedent's parents at the scene along with a 33-fl oz bottle filled with poppy seeds and water.

### *Case 2*

A 21-year-old white male college student living in a fraternity house was found deceased lying on his bed within his room by a roommate. He had foam at his nose and mouth. There were no injuries. A prescription bottle for Adderall was found in his room. There were no alcohol containers or other drugs at the scene. He was last known to be alive the previous evening. The decedent's friend stated that he received messages from the decedent; the first one stating that the decedent did a "double wash" of a big bag and was nodding off, but was trying to keep himself from falling asleep. A second message sent 2 min later said that this was the most opiates he ever consumed. A third message sent 2 min later stated that the decedent was nervous and that he had slowed breathing and a very weak pulse. The friend also had a missed phone call from the decedent 7 min after the last message. The decedent's friend stated that he knew the decedent had used poppy seeds before, but had never overdosed in the past. The decedent and his friend would go to the grocery store and buy a bulk bag of poppy seeds. They would put the seeds in water and shake it, and would drink the water that was drained. A "double wash" is when the poppy seeds had been shaken in water twice and the water ingested. The friend stated that the seeds he had used were really strong and that he drank <1/3 of his normal amount and that if he had drunk his normal amount, he would have overdosed. Femoral blood contained >0.80 mg/L morphine and 0.26 mg/L codeine. Vitreous contained 0.46 mg/L morphine and 0.26 mg/L codeine. No 6-acetylmorphine was detected. Autopsy revealed pulmonary edema and early acute pneumonia.

## Materials and Methods

### *Reagents and Materials*

Morphine-, codeine-, and thebaine-certified reference standards (1 mg/mL in methanol) were purchased from Cerilliant Corporation (Round Rock, TX). Morphine-$d_3$ (1 mg/mL in methanol) was obtained from Sigma-Aldrich (St. Louis, MO). Acetonitrile (Optima® LC-MS grade) was obtained from Fisher Scientific (Fair Lawn, NJ). Formic Acid was obtained from Sigma-Aldrich. Methanol was obtained from J.T. Baker (Phillipsburg, NJ). Water was purified with a Millipore Direct-Q® 3 UV Water Purification System (Billerica, MA). Kendall Monoject™ 3-mL Luer Lock syringes were obtained from Tyco Healthcare (Dublin, Ireland). Polytetrafluoroethylene (PTFE) syringe filters (13 mm) with a 0.45-μm pore size were obtained from VWR International (Radnor, PA). Lemon juice was purchased locally.

A total of 22 poppy samples were purchased from online sources: bulk poppy seeds ($n$ = 19), poppy seed powder ($n$ = 1), poppy seed tea bags ($n$ = 1), and liquid poppy extract ($n$ = 1) as described in Table 1. Of the bulk poppy seeds, three samples with different harvest dates were purchased from one vendor, and two samples with different harvest dates were purchased from a separate vendor, to examine differences within a brand.

### *Instrumentation*

Nitrogen evaporation of internal standard (IS), calibrators, and quality controls (QCs) was performed with a Caliper Life Sciences TurboVap® LV Concentration Workstation (Hopkinton, MA). Analytes were separated and quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS) with an Agilent 1290 Infinity II liquid chromatograph coupled to an Agilent 6470 triple quadrupole mass spectrometer (Santa Clara, CA). Agilent MassHunter Workstation software (version B.07, Santa Clara, CA) was used for data acquisition and analysis.

### *Preparation of Standard Solutions*

A morphine-$d_3$ IS solution was prepared at 1000 ng/mL in methanol. Mixed analyte calibrator solutions were prepared for morphine, codeine, and thebaine in methanol by serial dilution from 5000 to 2500 ng/mL, 1000, 500, 250, 100, and 10 ng/mL. A 20-μL aliquot of each calibrator solution was combined with 20 μL of IS solution. A negative control sample was also prepared with 20 μL of IS solution. All calibrators were dried down under nitrogen and reconstituted with 200 μL of 95:5 (v/v) mobile phase. Final calibrator concentrations were 1, 5, 10, 25, 50, 100, 250, and 500 ng/mL.

Mixed analyte QC solutions were prepared separately for morphine, codeine, and thebaine in methanol by serial dilution from 4000 to 750 ng/mL and 25 ng/mL. A 20-μL aliquot of each QC solution was combined with 20 μL of IS solution. All QCs were dried down under nitrogen and reconstituted with 200 μL of 95:5 (v/v) mobile phase. Final QC concentrations were 2.5 ng/mL (low), 75 ng/mL (medium), and 400 ng/mL (high).

### *Sample Preparation and Extraction*

Water was used for extraction under neutral conditions. For the bulk poppy seeds, 150 mL of water was added to 85 g of seeds. For the poppy seed tea bags, 30 mL of water was added to the contents of two bags (6 g). For the poppy seed powder, 100 mL of water was added to 35 g of powder. For the liquid poppy extract, 13 mL of water was added to 7 mL of extract (equivalent to 4 g of seeds, according to the vendor). These mixtures were gently stirred by hand for 10 sec every 30 sec during a 10-min period at room temperature (23°C). Poppy seed teas were also prepared using water preheated to 94°C to mimic brew recipes found online.

Poppy Seed Wash (the vendor for sample 2) recommends on their Web site that new users start with a 2–3 oz dose of poppy seeds. In addition, poppy seed tea users on the Internet recommend adding just enough water to cover the seeds in a tea-making container. Beakers were used for making the teas in the present study. A weight of 85 g (3 oz) was chosen for all bulk poppy seed extractions to reflect Poppy Seed Wash's recommendation for seed mass. In addition, 150 mL water was the volume

TABLE 1—*Inventory of poppy samples with product information provided by the vendors at the time of purchase. "Not specified" indicates lack of available information on product packaging.*

| Sample ID # | Vendor | Origin Claimed on Packaging | Use By Date on Packaging | Plant Type Claimed on Packaging | Other Information |
|---|---|---|---|---|---|
| 1 | TerraVita | Canada | Nov 2021 | California Poppy | Poppy Seed Tea Bags |
| 2 | Poppy Seed Wash | Not specified | Not specified | *P. somniferum* | Unwashed |
| 3 | Dual Spices | Holland | Feb 2018 | Not specified | |
| 4 | Medley Hills Farm | Ohio | 5/29/2017 | Blue | |
| 5 | International Spice | Spain | 11/2018 | Not specified | Unwashed |
| 6 | Frontier Co-Op | Not specified | Not specified | *P. somniferum* | |
| 7 | Sincerely Nuts | U.K. | 2/16/2017 | Not specified | |
| 8 | Bob's Red Mill | Not specified | 8/27/2018 | Not specified | |
| 9 | Natural Traders Co | Turkey | Jan 2019 | Blue | |
| 10 | Food to Live | England | Dec 2018 | Not specified | |
| 11 | Anna and Sarah | Holland | May 2018 | Blue | Unwashed |
| 12 | Nature's Gourmet Classics | Not specified | 10/27/2017 | Not specified | Unwashed |
| 13 | Spicy World | Not specified | Not specified | Black | |
| 14 | We Got Nuts | Not specified | Jun 2017 | Not specified | |
| 15 | Herb Pharm | Not specified | Jul 2021 | *E. californica* | Liquid extract (400 mg/0.7 mL) |
| 16 | Tasmanian Connoisseurs | Tasmania | Not specified | Tasmanian strain | Unwashed |
| 17 | We Know Seeds | Afghanistan | Not specified | Afghan Blue *P. somniferum* | Unwashed |
| 18 | Nodding Turtle | Afghanistan | Not specified | Afghan Blue *P. somniferum* | |
| 19 | Federal Ingredients | U.S.A. | Oct 2019 | Not specified | Poppy seed powder |
| 20 | Sincerely Nuts | U.K. | 2/11/2017 | Not specified | Unwashed |
| 21 | International Spice | Spain | 3/28/2018 | Not specified | |
| 22 | Sincerely Nuts | U.K. | 8/2/2017 | Not specified | Unwashed |

that covered the seeds in the beakers. Due to the limited supply of poppy seed tea bags, poppy seed powder, and liquid poppy extract, four equal portions of these samples were allocated for the four extractions performed in the present study. Extraction volumes were adjusted for the contents of the poppy seed tea bags as well as the poppy seed powder.

Water acidified with lemon juice (5%) was used for extraction under acidic conditions to mimic taste modifiers described on forums and in tea reviews. For the bulk poppy seeds, 142.5 mL of water and 7.5 mL of lemon juice were added to 85 g of seeds. For the poppy seed tea bags, 28.5 mL of water and 1.5 mL of lemon juice were added to the contents of two bags (6 g). For the poppy seed powder, 95 mL of water and 5 mL of lemon juice were added to 35 g of powder. For the liquid poppy extract, 12 mL of water and 1 mL of lemon juice were added to 7 mL of extract (equivalent to 4 g of seeds, according to the vendor). These mixtures were gently stirred by hand for 10 sec every 30 sec during a 10-min period at room temperature and with acidified water preheated to 94°C.

All poppy samples ($n = 22$) were initially extracted under neutral conditions at room temperature. Supernatants were drawn into Luer Lock syringes and expressed through PTFE syringe filters. Triplicate aliquots were diluted 1:2000 in 95:5 (v/v) mobile phase. After drying down 20 µL of IS solution, 200 µL of each extract dilution was used for reconstitution. Depending on alkaloid content, subsequent dilutions at 1:10, 1:50, 1:150, 1:200, 1:1000, and 1:5000 were prepared and analyzed when appropriate in cases of analyte quantification outside of the calibration curve. The optimal dilutions for each sample were used for each of the four extractions.

### *Liquid Chromatography*

Separations were performed using gradient elution at 0.4 mL/min with 0.1% formic acid in water (mobile phase A) and 0.1% formic acid in acetonitrile (mobile phase B) on an Agilent ZORBAX Eclipse Plus C18 column (1.8 µm, 2.1 × 50 mm). The gradient began with a 1-min hold at 5% B, increased to 30% B over 2 min, increased to 95% B in 0.10 min, held at 95% B for 1.30 min, then back to 5% B in 0.10 min followed by a 1.10-min post time for re-equilibration. An injection volume of 2 µL was used.

### *Mass Spectrometry*

Analyte MS parameters were optimized using flow injection of individual 100 ng/mL analyte solutions in 50:50 A:B mobile phase with MassHunter Optimizer software (Agilent). Optimized LC-MS/MS parameters are presented in Table 2. For optimization of ion source parameters, a 100 ng/mL mixed analyte solution in 95:5 A:B mobile phase was used with column separation and MassHunter Source Optimizer software. The capillary voltage was set to 2000 V, the drying gas (nitrogen) temperature and flow were 300°C and 6 L/min, the nozzle voltage was set to 0 V, the sheath gas (ultrapure nitrogen) temperature and flow were 350°C and 11 L/min, and the nebulizer was set to 45 psi. Data were acquired in multiple reaction monitoring mode using positive electrospray ionization.

### *Method Validation*

Method validation parameters were assessed in accordance with Scientific Working Group for Forensic Toxicology (SWGTOX) standard practices (18). Overall linearity was assessed by least squares regression with $1/x^2$ weighting using eight nonzero calibrators over four validation batches and subsequent sample batches for a total of 15 batches. Linearity was acceptable when $R^2 \geq 0.99$ and calibrators quantified within ±20% of the target concentration.

Overall accuracy and precision were determined from 27 replicates of the low, medium, and high QC over four validation batches and 11 sample batches. Accuracy was determined as % target concentration, and precision is expressed as % CV. Accuracy was acceptable if within ±20% of the target concentration. Precision was acceptable if % CV was within 15%.

Matrix effects were determined using filtered tea extracts from two low-concentration bulk poppy seed samples, the liquid extract sample, and the powder sample. These extracts were

prepared with heated water acidified with lemon juice and diluted in 95:5 (v/v) mobile phase to either 1:2000 or 1:5000, depending on the alkaloid content in the sample. A 200-μL aliquot of each extract was added to tubes containing dried-down IS and analytes at both low and high QC levels in duplicate. Peak responses for morphine ($n$ = 4), codeine ($n$ = 4), thebaine ($n$ = 6), and morphine-$d_3$ ($n$ = 8) prepared in tea matrix were compared with peak responses for morphine ($n$ = 8), codeine ($n$ = 8), thebaine ($n$ = 8), and morphine-$d_3$ ($n$ = 8) in neat QC solutions to determine matrix effects at both low and high concentrations. Values greater than 100% indicate ion enhancement while values <100% indicate ion suppression.

Dilution integrity was assessed by diluting mixed analyte solutions from 0.1 mg/mL to both 50 ng/mL (1:2000, $n$ = 9) and 20 ng/mL (1:5000, $n$ = 9). Dilutions were acceptable if analytes quantified within ±20% of the expected concentration. Carryover was assessed by injecting a negative control sample containing only 100 ng/mL IS immediately after a mixed analyte sample at 2.5 times the high QC (1000 ng/mL). The absence of analyte signal above the LOQ confirmed the absence of carryover.

## Results

The optimized method was validated and met acceptable criteria prior to sample analysis. The LOQ was 1 ng/mL for morphine, codeine, and thebaine. Linear ranges are presented in Table 3 and were 1–500 g/mL for all analytes. $R^2$ were ≥0.99 for all calibration curves (Table 3). Accuracy, precision, and matrix effect results are presented in Table 4. Overall accuracy ranged from 92.3% to 103.4%, and overall precision ranged from 4.2% to 7.7% CV. Matrix effects were minimal (95.1–103.7%). Dilution integrity was acceptable for both dilution factors. Morphine, codeine, and thebaine quantified within 94.4–117.1%, 82.0–97.8%, and 101.9–119.0% of target, respectively.

Twenty-two poppy samples were prepared with four brew recipes (room temperature and heated water, with and without acid modifier) and analyzed via a validated LC-MS/MS method for quantification of morphine, codeine, and thebaine. Sample 1 was the contents of two poppy seed tea bags (6 g). Sample 15 was the liquid poppy extract (equivalent to 4 g of seeds, according to the vendor). Sample 19 was the poppy seed powder (35 g). Samples 2–14, 16–18, and 20–22 were the bulk poppy seeds (85 g each). Mean (±standard deviation) morphine, codeine, and thebaine concentrations for the 22 poppy samples are presented for the four extraction conditions in Figures 1–3. These data are also presented under Table S1. Concentrations (expressed as mg alkaloid per kg seeds) were obtained from calibration curves, also taking into account dilutions, volume of water in tea, and weight of poppy used. Morphine, codeine, and thebaine concentrations ranged from <1–2788 mg/kg, <1–247.6 mg/kg, and <1–124 mg/kg, respectively, between all extractions. Morphine, codeine, and thebaine were not detected in the liquid poppy extract (sample 15).

Overall mean sample concentrations ($n$ = 22) of morphine, codeine, and thebaine from the room temperature neutral extraction were compared separately to those from the room temperature acidic, heated neutral, and heated acidic extractions. A paired 2-sample $t$-test for means was used to test for significance at a 95% confidence level with 21 degrees of freedom. The null hypothesis was that no difference existed between the means. A $p$-value <0.05 indicated a significant difference between the means. Two-tailed $p$-values from this test are presented in Table 5. Mean morphine and codeine concentrations were only significantly different ($p$-values of 0.01 and 0.001, respectively) when extracted under heated acidic conditions compared with room temperature neutral conditions. Thebaine concentrations were significantly different when extracted under both room temperature acidic and heated acidic conditions ($p$-values of 0.0001 and 0.00007, respectively) compared with room temperature neutral conditions. Thebaine concentrations were significantly different when extracted under both room temperature acidic and heated acidic conditions ($p$-values of 0.0001 and 0.00007, respectively) compared with room temperature neutral conditions.

## Discussion and Conclusion

An analytical method for quantification of morphine, codeine, and thebaine from home-brewed poppy seed tea was successfully developed, validated, and applied to the analysis of 22 poppy samples. It was important to include thebaine in the current

TABLE 2—*Optimized liquid chromatography-tandem mass spectrometry parameters for morphine, codeine, thebaine, and morphine-$d_3$.*

| Analyte | Q1 Ion (m/z) | F (V) | Q3 Ion (m/z) | CE (V) | D (ms) | CA (V) | RT (min) | IS |
|---|---|---|---|---|---|---|---|---|
| Morphine | *286.3* | 156 | *152* | 68 | 15 | 7 | 0.662 | Morphine-$d_3$ |
| | 286.3 | 156 | 165 | 48 | 15 | 7 | | |
| Codeine | *300.4* | 156 | *152* | 76 | 15 | 7 | 2.025 | Morphine-$d_3$ |
| | 300.4 | 156 | 165 | 48 | 15 | 7 | | |
| Thebaine | *312.4* | 88 | *58.1* | 20 | 15 | 7 | 3.059 | Morphine-$d_3$ |
| | 312.4 | 88 | 152 | 76 | 15 | 7 | | |
| Morphine-$d_3$ | *289.5* | 136 | *152* | 72 | 15 | 7 | 0.657 | — |
| | 289.5 | 136 | 168.1 | 44 | 15 | 7 | | |

Ions in italics indicate quantifying transition.
Q1, quadrupole 1; F, fragmentor; Q3, quadrupole 3; CE, collision energy; D, dwell; CA, cell accelerator; RT, retention time; IS, internal standard.

TABLE 3—*Calibration range and linearity for morphine, codeine, and thebaine.*

| Analyte | Calibration Range (ng/mL) | $y$-Intercept (Mean ± SD, $n$ = 15) | Slope (Mean ± SD, $n$ = 15) | $R^2$ (Range, $n$ = 15) |
|---|---|---|---|---|
| Morphine | 1.0–500 | 0.001 ± 0.001 | 1.755 ± 0.142 | 0.998–1.000 |
| Codeine | 1.0–500 | 0.002 ± 0.001 | 1.754 ± 0.170 | 0.991–0.999 |
| Thebaine | 1.0–500 | −0.011 ± 0.008 | 13.296 ± 0.966 | 0.991–0.999 |

SD, standard deviation.

TABLE 4—*Overall accuracy, precision, and matrix effects data for morphine, codeine, and thebaine in poppy tea. Overall matrix effects for morphine-$d_3$ (internal standard, IS) are included.*

| | Analyte | | | |
|---|---|---|---|---|
| Method Validation Results | Morphine | Codeine | Thebaine | Morphine-$d_3$ |
| Overall accuracy | | | | |
| Low* (%, $n$ = 27) | 92.3 | 92.8 | 93.3 | – |
| Med† (%, $n$ = 27) | 101.9 | 96.7 | 96.1 | – |
| High‡ (%, $n$ = 27) | 103.4 | 94.0 | 100.4 | – |
| Overall precision | | | | |
| Low* (%, $n$ = 27) | 5.7 | 7.7 | 7.3 | – |
| Med† (%, $n$ = 27) | 4.7 | 4.2 | 7.1 | – |
| High‡ (%, $n$ = 27) | 4.8 | 5.1 | 6.1 | – |
| Overall matrix effects§ | | | | |
| Low* | 102.3 | 100.9 | 103.7 | 95.1 |
| High‡ | 101.3 | 98.7 | 101.0 | 100.6 |

*Low concentrations were 2.5 ng/mL for morphine, codeine, and thebaine. IS concentration of 100 ng/mL.

†Med concentrations were 75 ng/mL for morphine, codeine, and thebaine. IS concentration of 100 ng/mL.

‡High concentrations were 400 ng/mL for morphine, codeine, and thebaine. IS concentration of 100 ng/mL.

§Matrix effects were assessed in heated poppy tea modified with lemon juice.

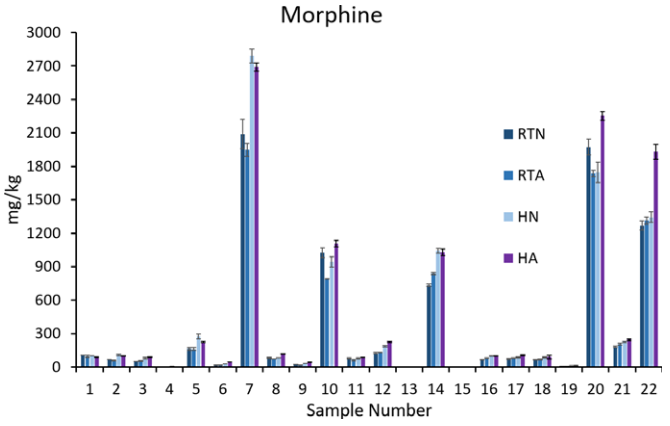


FIG. 1—*Mean (±standard deviation,* n = *3) morphine concentrations (mg morphine/kg seeds) after extraction under room temperature neutral (RTN), room temperature acidic (RTA), heated neutral (HN), and heated acidic (HA) conditions for 22 poppy seed samples.*

method because a trace amount of thebaine was present in the decedent's blood from Case Report 1 at autopsy and helps identify morphine source. Dilution integrity for the current method was confirmed at both 1:2000 and 1:5000 for all analytes, and the calibration range (1–500 ng/mL) was sufficient to quantify alkaloid content in poppy seed teas, allowing for determination of alkaloid content on seed coats.

Morphine, codeine, and thebaine concentrations varied greatly among the 22 seed samples. When examining differences between extraction techniques, acidic extractions significantly increased thebaine yield compared to neutral extractions (19). Thebaine's polarity is very slight, which gives thebaine low solubility in water (19). Extracting thebaine in an acidic

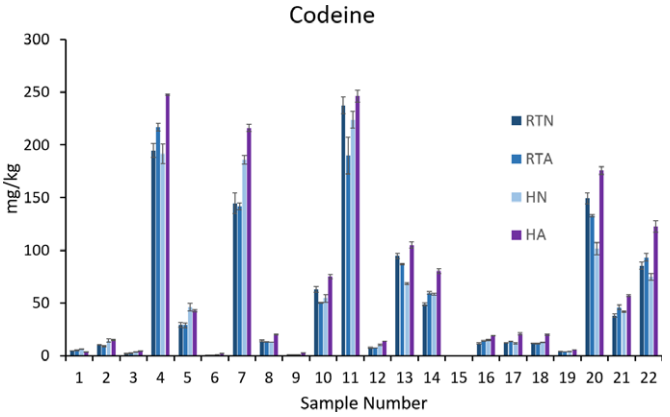


FIG. 2—*Mean (±standard deviation,* n = *3) codeine concentrations (mg codeine/kg seeds) after extraction under room temperature neutral (RTN), room temperature acidic (RTA), heated neutral (HN), and heated acidic (HA) conditions for 22 poppy seed samples.*

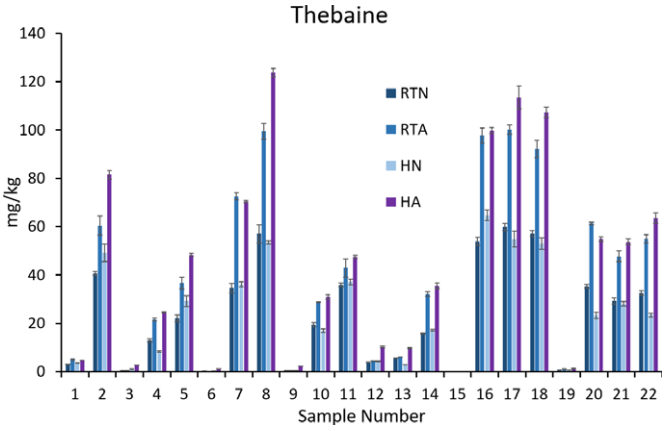


FIG. 3—*Mean (±standard deviation,* n = *3) thebaine concentrations (mg thebaine/kg seeds) after extraction under room temperature neutral (RTN), room temperature acidic (RTA), heated neutral (HN), and heated acidic (HA) conditions for 22 poppy seed samples.*

TABLE 5—*Two-tailed* p*-values obtained for morphine, codeine, and thebaine from comparison of overall room temperature acidic (RTA), heated neutral (HN), and heated acidic (HA) analyte concentrations to overall room temperature neutral (RTN) analyte concentrations* (n = *22) using a paired 2-sample* t*-test for means. A* p*-value <0.05 indicates a significant difference between the means. Significant* p*-values are bolded.*

| | $p$-Value (Two-Tail) | | |
|---|---|---|---|
| Analyte | RTA Versus RTN | HN Versus RTN | HA Versus RTN |
| Morphine | 0.2 | 0.2 | **0.01** |
| Codeine | 0.5 | 0.7 | **0.001** |
| Thebaine | **0.0001** | 0.6 | **0.00007** |

environment increases thebaine's affinity for aqueous solutions. This explains why acidic extractions were most effective at increasing thebaine yield.

A heated acidic extraction significantly increased both morphine and codeine yields compared to room temperature neutral. Although the heated neutral and room temperature acidic extractions did not yield significant differences alone in morphine and

codeine compared to the room temperature neutral extraction, it is possible that the heated and acidic factors combined caused a significant increase in morphine and codeine yield. According to The Merck Index, 1 g of morphine dissolves in 5000 mL of room temperature water and 1100 mL of boiling water (20). Morphine is more polar than thebaine, but morphine still lacks affinity for water. This might be explained by morphine's competing acidic and basic functional groups. In an acidic environment such as the 5% lemon juice tea, morphine's tertiary amine would be protonated, but it is possible that morphine's preference for heated water could still be inhibiting room temperature acidic extractions. Increased water solubility and pKa could contribute to increased morphine yield in the heated acidic teas. According to the Merck Index, codeine monohydrate, codeine hydrochloride, codeine sulfate, and codeine phosphate are all more soluble in boiling water than room temperature water (20). This information was not given for codeine base, but it can be assumed that codeine base is more soluble in boiling water as well. Codeine's tertiary amine should also protonate in acidic environments. Like morphine, codeine concentrations were only significantly different in the heated acidic extraction.

Alkaloid content varied both between vendors and between harvest dates, as expected. Despite the variation in alkaloid content between harvest dates, samples 7, 20, and 22 had the highest concentrations of morphine regardless of extraction method used in this study. The morphine yielded from samples 7, 20, and 22 during each extraction (ranging from 108–237 mg) would correlate with lethal doses if moderate volumes of tea were consumed. While this study used 85 g of seeds, online recipes call for 1–2 lb (or 454–908 g), which means that preparing tea with samples 7, 20, and 22 could produce 577–2532 mg of morphine if scaled up accordingly. Samples 10 and 14, although from different vendors, also contained high concentrations of morphine. The morphine yielded from samples 10 and 14 during each extraction ranged from 62.3–94 mg. It is unlikely that lethal doses of codeine would be obtained from poppy seed tea due to both codeine's weak analgesic properties and its low abundance in opium latex. It could be possible to obtain a lethal dose of codeine if enough poppy seed tea were consumed. However, the morphine consumed from poppy seed tea poses a greater risk to consumers due to both its strong analgesic properties and its high abundance in opium latex.

Morphine, codeine, and thebaine were not detected in sample 15 (the liquid poppy extract) for all extractions. This was expected because the bottle label specifically stated that the extract was produced from whole flowering *Eschscholzia californica* (California poppy) plants which contain different alkaloids. However, the product information for sample 1 (the poppy seed tea bags) was more ambiguous. These tea bags came in a package that stated "Poppy Seed (California) Tea" and "Ingredients: Poppy" on the label. The vendor claimed these seeds were of Canadian origin. It is unclear if the vendor intended to sell these as *E. californica* seeds, but the detection of morphine, codeine, and thebaine in sample 1 for all extractions is consistent with *P. somniferum* seeds.

The plant sources claimed by other vendors were either vague (for example, "blue"), specific ("*Papaver somniferum*"), or not stated at all. All other samples were suspected to originate from the opium poppy. Morphine, codeine, and thebaine were detected in all bulk poppy seeds and the poppy powder as well. Morphine concentrations were higher than codeine in all samples except for samples 4, 11, and 13. Morphine concentrations were also higher than thebaine in all samples except for samples 4 and 13. In samples 4, 11, and 13, morphine concentrations were 2.6–6.0, 61–86.8, and 0.356–0.65 mg/kg, respectively, for all extractions. Codeine concentrations were 192–247.6, 190–246, and 68.4 mg/kg, respectively, for all extractions. Thebaine concentrations were 8.3–24.5, 35.9–47.5, and 2.85–9.8 mg/kg, respectively, for all extractions. The Merck Index states that codeine and thebaine have abundances in opium latex of 0.7–2.5% and 0.3–1.5%, respectively (20). It is also known that cultivators will breed opium poppies to increase the yield of certain alkaloids in their crops depending on demand (21). The source plants for samples 4, 11, and 13 could have been products of this practice from generations of selection in opium poppy cultivation because in general, morphine is the most abundant alkaloid in opium latex (20).

Previous poppy seed administration studies utilized seeds with known alkaloid content determined by analytical extractions using laboratory chemicals (14–16). However, most individuals use home-brewing methods such as water rinses. Alkaloid content in materials purchased over the Internet is unknown, and no peer-reviewed literature has examined the concentrations of morphine and codeine that can result from home-brewed poppy tea. The present study replicated home-brew extractions published online by poppy seed tea abusers. Alkaloid content in poppy seeds from this study was similar to previous literature (14–16). However, higher concentrations of both morphine and codeine (2788 and 247.6 mg/kg, respectively) were detected in some samples examined in this study, due to the wider sample variety. The data from the present home-brew study, when compared with data from previous studies, suggest that home-brew extractions can be just as effective at rinsing opium alkaloids from poppy seed coats as analytical extractions with laboratory chemicals.

Although some bulk poppy seeds can be more lethal than others due to the variation in morphine concentrations both between vendors and between harvest dates, it should be noted that regardless of sample, it is possible to obtain lethal doses of morphine from poppy seed tea if moderate volumes of tea are consumed. Most poppy seed tea users fill their tea-making containers (such as water bottles) with just enough water to cover the seeds. This is why an extraction volume of 150 mL was chosen for the 85 g of seeds per sample used in this study. However, it is common for poppy seed tea users to use greater masses of seeds (such as 1–2 lb, or 454–908 g) and greater volumes of water for their extractions at home.

It should also be noted that poppy seed tea users' sensitivity to morphine's analgesic effects will vary based on individual tolerances. A lethal dose of morphine for an individual with a high opioid tolerance due to previous opioid use may not be the same as a lethal dose for an opioid-naïve individual. However, this does not guarantee an opioid-tolerant user's safety when consuming a large volume of poppy seed tea. Barring analytical testing, there is no means for the average individual to know how much morphine is in a bag of poppy seeds they just purchased, even if the individual has previously ordered from that vendor. Any time an individual consumes poppy tea made from seeds and other poppy products, the individual is assuming the risks involved with this practice.

The described study was limited to examining only water temperature and pH when considering brewing techniques. However, additional parameters could be assessed in future studies. Most poppy seed tea users agitate their brews for 10–40 min. A 10-min agitation was chosen for this study, but future studies should incorporate longer agitation periods to assess correlation with final alkaloid yield. Additional experiments should also

replicate the straining techniques used by poppy seed tea users, such as plastic bags with small holes poked through by needles. Repeat washes for samples should also be assessed because many poppy seed tea users do this as well.

The opium poppy and poppy straw are listed as Schedule II controlled substances in the United States, along with morphine and codeine (22). Opium poppy seeds are not currently scheduled. They are recognized as safe for human consumption by the FDA (23). Sproll et al. (12) stated that poppy seeds are typically consumed in small quantities in baked goods, such as 3 g of seeds in a poppy seed bun. These quantities may not pose a risk to consumers, which might explain the FDA's opinion regarding poppy seed safety. However, the high morphine concentrations found in some samples in the present home-brew study indicate a substantial risk to consumers if moderate amounts are consumed. Although poppy seeds are not currently controlled in the United States (and in other countries such as Canada), it is possible that regulations might be implemented in the future as poppy seed tea abuse becomes more of a public safety concern. As with many drug abuse practices, the diversion of poppy seeds may not ever be completely eradicated. However, the lack of regulations in the poppy seed market as well as the ease of making home-brewed poppy seed tea demonstrates a need to further study the health risk of *P. somniferum* seeds.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1**. Mean morphine concentrations expressed as mg alkaloid per kg seeds after extraction under room-temperature neutral (RTN), room-temperature acidic (RTA), heated neutral (HN), and heated acidic (HA) conditions with standard deviations (SD).