Detection of Undeclared Halogen Substituted Drug Compound in a Natural Health Product

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ABSTRACT

INTRODUCTION: The U-Dream line of products are marketed as natural health product sleep aids in Canada and as dietary supplements in the United States. Several user reviews of the product mention concerning side effects not typically associated with the listed herbal ingredients stated on the product label. Based on these concerns an analytical study was undertaken to determine if the products contained any undeclared pharmaceuticals.

METHODS: Product was screened by high resolution mass spectrometry (HRMS) for known pharmaceuticals with sedative and sleep promoting properties. Based on the mass spectral screens an unknown compound was isolated for characterization by nuclear magnetic resonance (NMR) and presence confirmed by Enzyme-linked Immunosorbent Assay (ELISA).

RESULTS: The mass spectral analyses indicated the presence of an undeclared analogue of the pharmaceutical drug zopiclone within the product lot tested. NMR characterization confirmed the compound to be a brominated analogue of zopiclone and a commercial zopiclone/eszopiclone ELISA kit tested positive.

DISCUSSION: The undeclared compound was found to be an analogue of zopiclone whereby the chlorine atom was substituted with bromine. Given the results of the ELISA assay and the structural similarity to zopiclone it is likely the compound exhibits biological activity. Of considerable concern is not only the potential of the unknown compound to exhibit pharmacological activity, but the lack of a safety profile by which the risk can be properly assessed.

CONCLUSIONS: The natural health product regulations provide a framework for high quality, safe and efficacious products to access the market. It is the responsibility of the manufacturer to assure traceability and transparency in their supply chain and establish verifiable compliance with GMP. This study illustrates the importance of careful evaluation of analytical data in order to detect undeclared adulterants and highlights the need for an active monitoring and surveillance system for potentially high-risk products.

KEYWORDS: Adulteration; herbal sleep-aid; natural health product; zopiclone

Introduction

Natural Health Products (NHPs) in Canada are defined and subject to the requirements set out in the Natural Health Products Regulations and include vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines, probiotics and other products like amino acids and essential fatty acids and are restricted to oral, topical or sublingual routes of administration [1].
These products cannot be prescription products, drugs administered by puncturing the skin or any substance that is regulated under the Tobacco or the Controlled Drugs and Substances Acts of Canada [2]. Although these products are considered a subset of drugs, they are exempt from many of the requirements in the Food and Drugs Regulations unless specifically referenced in the Natural Health Products Regulations under the authority of the Natural and Non-prescription Health Products Directorate (NNHPD) [1]. All manufacturers, packagers, labellers and importers of natural health products are required to hold a site license, for which they must demonstrate that they are in compliance with the Good Manufacturing Practices (GMP) requirements set out in the regulations [1]. NHPs are required to undergo a premarket approval process and obtain a license prior to entering the market [1].

Under the existing regulatory framework post-market activities for NHPs are predominately risk-based and complaint driven. In a Health Canada report published in 2016, it recommended the use of proactive tools including inspections to balance the current paper-based licensing process [3]. While Health Canada does engage in a number of post-market activities to limit potential health risks to Canadians, the 2016 report acknowledges that challenges remain with the largely reactive approach, recommending conducting on-site inspections, more laboratory testing as part of compliance

Figure 1. List of U-Dream products licensed as natural health products in Canada as of August 23, 2019 as shown in the NNHPD’s Licensed Natural Health Product Database [17].
verification, and the need for stronger post-market authority [3].

Overall NHPs are low risk, can be beneficial and are generally safe, when manufactured in accordance with good manufacturing practices and used as recommended [4–8]. However, adulteration, whereby products contain substances that are not declared on the label but were intentionally added during manufacture, can raise the risk associated with NHP use [3, 9–16]. The presence of undeclared pharmaceuticals has been reported in the literature, in particular with products marketed for weight loss, sports performance/muscle building, sexual performance and to a lesser degree sleep problems, inflammatory conditions and metabolic diseases [10–16].

The U-Dream line of products are licensed natural health products (NHPs) marketed in Canada by Biotrade Canada Ltd. and are sold as over the counter sleep aids (Figure 1) [17]. As of October 10 2019, the U-Dream Full Night product with Natural Health Product Number (NPN) 80070691 holds the #3 Amazon Bestsellers Rank in Medicinal Sleep Aids [18]. As of August 23rd, 2019, this line of products is also present as a dietary supplement in the United States through amazon.com [19].

The product is purported to be an all-natural herbal medicine consisting of several botanical extracts and L-tryptophan. There are different formulations of the U-Dream product on the Canadian market with slight differences in presence and levels of declared herbal medicinal ingredients; as an example the medicinal ingredients for the U-dream Full product with NPN 80088078 and U-Dream Full with NPN 80070691 are shown in Tables 1 and 2. All U-Dream products state they are 100% natural, and products with different NPN license numbers have essentially the same external packaging color, style, and design.

The U-Dream products have found significant success in the market with many reviews touting their effectiveness as a sleep aid. However, some testimonials associated with the product are concerning such as consumers describing symptoms not typically associated with the listed ingredients, reports that the product left a metallic taste in the mouth following ingestion with others describing serious withdrawal symptoms after only short-term use [18, 19]. These effects are not included in the cautions or risk warnings for the product and are more typically associated with prescription pharmaceuticals rather than an over-the-counter NHP. With concerns for the risk to public health, an investigation of the product to screen for undeclared pharmaceutical ingredients was initiated with an initial focus on known prescription drugs used to treat insomnia such as Lorazepam. Preliminary screens of the product did not detect known pharmaceutical sleep aids but more detailed analysis indicated the presence of an unknown suspicious compound. This paper describes the further analytical efforts made to determine the identity of this unknown, undeclared compound.

### Methods

Solvents and reagents for the analytical work (Formic acid, LC grade methanol, acetonitrile) were purchased from VWR (Edmonton, AB, CAN), Sigma-Aldrich (Oakville, ON, CAN) and Fisher Scientific (Ottawa, ON, CAN). U-dream capsules were obtained from a local store in Burnaby, British Columbia, Canada. Two products were obtained, U-Dream Full 450 mg, NPN 80088078, lot number UDF008 and U-Dream Full, NPN 80070691, lot number UDF004.

### Mass Spectral Analysis for Lorazepam

An intact sealed capsule was removed from the product package and analyzed for the presence of lorazepam. Approximately 100 mg of powder was extracted in acetonitrile:water (1:1) using sonication followed

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**Table 1.** Medicinal ingredients listed in U-Dream full 450 mg product with NPN 80088078.

| Medicinal ingredient                       | Quantity per capsule |
|-------------------------------------------|----------------------|
| Passiflora incarnate 8:1 extract          | 110.0 mg             |
| Hesperidin                                | 85.5 mg              |
| Eriobotrya japonica 8:1 extract           | 65.0 mg              |
| Ziziphus jujube 10:1 extract              | 45.0 mg              |
| Hericium erinaceus 8:1 extract            | 30.0 mg              |
| L-Tryptophan                              | 30.0 mg              |
| Schisandra chinensis 7:1                  | 25.0 mg              |
| Curcumin                                  | 18.0 mg              |
| Reynoutria multiflora 5:1 extract         | 15.0 mg              |
| Rehmannia glutinosa 5:1 extract           | 15.0 mg              |

**Table 2.** Medicinal Ingredients Listed in U-Dream Full product with NPN 80070691.

| Medicinal Ingredient                       | Quantity per capsule |
|-------------------------------------------|----------------------|
| Passiflora incarnate 8:1 extract          | 110.0 mg             |
| Eriobotrya japonica 15:1 extract          | 65.0 mg              |
| Ziziphus jujube 10:1 extract              | 45.0 mg              |
| Hericium erinaceus 8:1 extract            | 30.0 mg              |
| Schisandra chinensis 7:1                  | 35.0 mg              |
| L-Tryptophan                              | 30.0 mg              |
| Reynoutria multiflora 5:1 extract         | 15.0 mg              |
| Rehmannia glutinosa 5:1 extract           | 15.0 mg              |
by centrifugation and filtration. A duplicate sample was prepared from the same capsule. A third aliquot was prepared in the same manner after spiking with a lorazepam certified reference material at 500 μg/g. The aliquots were analyzed on an Agilent 1290 HPLC coupled to an Agilent 6540 Accurate Mass Q-ToF (Agilent Technologies, Mississauga, ON, CAN) running in Auto MS/MS mode. The gradient conditions are as follows: 95/5 H₂O-MeCN to 95% MeCN over 12 minutes, hold for 1 min at 95% MeCN, return to initial gradient conditions and equilibrate for 4 minutes at a flow rate of 0.5 ml/minute. Separation is achieved on an Agilent Poroshell 120 SB-C18, 2.7 μm, 2.1 mm × 100 mm column (Agilent Technologies, Mississauga, ON, CAN) with a column temperature at 30°C. Data was analyzed against the Scripps Institute Metlin Accurate Mass (PCDL) Database (Scripps Research, La Jolla, CA, USA) set at 40°C using a gradient of 5% B at 0 min., 40% B at 6.0 min., 90% B at 9.3 min., 5% B at 10.0 min., 40% B at 6.0 min., 90% B at 9.3 min., 5% B at 10.0 min., with 0.1% formic acid as Mobile Phase A and 0.1% formic acid in methanol as Mobile Phase B. Injection volume was 10 μL with a flow rate of 1.6 mL/min and detector set to store signals at 210, 254, 280, 330 and 510 nm. The peak eluting at 5.2 min. was collected with a 0.2-μm syringe filter into HPLC vials. Samples were injected into an Agilent 1100 HPLC equipped with a quaternary pump, auto-sampler, column compartment, diode array detector and Gilson FC203B fraction collector. Separation was achieved with a Phenomenex Kinetex C18 5 μm, 100 × 4.6 mm column (Phenomenex, Torrance, CA, USA) using a gradient of 5% B at 0 min., 40% B at 6.0 min., 90% B at 9.3 min., 5% B at 10.0 min., with 0.1% formic acid as Mobile Phase A and 0.1% formic acid in methanol as Mobile Phase B. Injection volume was 10 μL with a flow rate of 1.6 ml/min and detector set to store signals at 210, 254, 280, 330 and 510 nm. The peak eluting at 5.2 min. was collected with the fraction collector programmed to collect in a time window from 5.1 to 5.7 min. Fractions from multiple runs were pooled together and dried under nitrogen for further evaluation.

A portion of the pooled isolated fraction was dissolved in chloroform-d and transferred through a glass wool filter to an NMR tube for analysis using a Bruker AVANCE 400 spectrometer equipped with Bruker Topspin software (Bruker, Ltd, Milton, ON, CAN). ¹H and two dimensional DFQ-COSY NMR experiments were conducted with chemical shift values presented in δ (ppm) and referenced to the residual solvent signal of CDCl₃. NMR data files were processed and analyzed using Mnova 11.0.4 (Mestrelab Research, Escondido, CA, USA).

Commercial zopiclone/eszopiclone ELISA kits were purchased from Neogen (Lexington, KY, USA). The U-dream samples were analysed using these kits as per
the manufacturer's instructions. Briefly the sample was dissolved in the EIA Buffer from the test kit. The samples were further diluted 1/10, 1/50, 1/100, and 1/200 as needed. Drug enzyme conjugates are added into each well along with samples, standards, or controls and incubated at room temperature for 45 min. Each well is then washed three times with 300 µL of wash buffer from the test kit. 100 µL of K-Blue substrate from the test kit is then added to each well and incubated for 30 minutes at room temperature. The enzyme reaction is stopped by adding 100 µL of Acid Stop and then gently mixed before measuring their absorbance at 450 nm using a Thermo Scientific Multoskan Go Variable Wavelength microplate reader (Thermo Fisher Scientific, Waltham, MA, USA).

Results

Mass Spectral Analysis for Lorazepam

Neither lorazepam nor lorazepam glucuronide were detected in the sample using the described method. Examination of the mass spectral acquisition analysis in Mass Hunter to find discrete chemical entities revealed the presence of a prominent peak showing a halogen isotope cluster suggesting the presence of a brominated compound (Figure 2).

HR-LCMS Screening for Undeclared Compounds

Full scan positive ESI data were acquired from each of the U-Dream products using the Q-Exactive Orbitrap. For both products lots, the compound detected in

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Full scan accurate mass spectrum of unknown peak showing characteristic bromine isotopic pattern.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Full scan mass spectrum of peak eluting at 3.9 minutes in the HR-LCMS Orbitrap analysis of the U-Dream product.
the initial screen was identified as a prominent peak at 3.94 min in the TIC. The full scan mass spectrum of this compound is shown in Figure 3. The spectrum shows the H⁺-adduct at 433.0620 m/z and the associated Na⁺-adduct at 455.0432 m/z as well as ions at 435.0589 m/z and 457.0410 m/z. The near 1:1 ratio and mass differences between these adducts and the ions at 435.0589 m/z and 457.0410 m/z provides strong evidence for the presence of a single bromine atom in this compound. This identification is further supported by the presence of similar isotopic ratios for other in-source fragmentation products observed in the full scan mass spectrum shown in Figure 3.

The theoretical mass spectra of several known halogen-containing compounds with sedative activity, were compared against the mass spectrum of the unknown compound. It was observed that the substitution of the bromine atom in the observed mass for the unknown compound with a chlorine atom would result in a mass of 389 g/mol. As the unknown compound is represented in the mass spectra as an H⁺-adduct at 433.0620 m/z and an Na⁺-adduct at 455.0432 m/z the target mass of the analogue drug would have a mass of 388 g/mol which is consistent with the known prescription drug zopiclone (monoisotopic mass 388.1051 g/mol), shown in Figure 4 along with the suggested structure of the unknown compound.

The major fragmentation m/z values for several chlorine-containing drug compounds were obtained from MassBank [20]. The reference data was then compared to the observed fragments from the unknown, recalculated to account for the substitution of the chlorine atom with a bromine atom. In Table 4 the calculated modified reference m/z values for zopiclone fragments is compared with the observed fragments in mass spectrum of the unknown compound, following MS² analysis on the 433 m/z product ion.

Retrospective analysis of the full spectrum scan for the peak also showed A+2 ions at near a 1:1 ratio, corresponding to the major m/z ions suspected to contain bromine atoms, including ions at 157.9, 184.9, 290.9, 291.9, 308.9, 322.9 and 391.0.

**Isolation, Structural Elucidation and Activity Testing of Undeclared Compound**

The pooled fraction isolated by HPLC containing the compound of interest was analyzed by NMR and the one-dimensional ¹H spectra is shown in Figure 5.

The presence of a large water signal at 1.6 ppm and several other signals indicated the fraction was not pure, however several hallmark signals were observed that are indicative of aromatic protons, consistent with the structure proposed in Figure 4. The NMR spectrum showed a series of doublets in the range of 7.95–8.92 ppm that were assigned to protons in pyridyl and pyrazinyl rings.

Table 4. Comparison of major m/z for zopiclone reported in Massbank [20], theoretical m/z for a zopiclone compound with its chlorine replaced with a bromine atom and observed m/z observed from the MS/MS analysis of the 433 m/z product ion in the U-Dream product.

| m/z (MassBank EQ364303) | Theoretical m/z Cl replaced with Br | m/z observed in U-Dream product |
|--------------------------|-----------------------------------|-------------------------------|
| m/z                      | Annotation                        | m/z                           | Annotation                           | m/z |
| 98.0835                  | C5H10N2+                          | 98.0835                       | C5H10N2+                              | 98.0843 |
| 99.0917                  | C5H11N2+                          | 99.0917                       | C5H11N2+                              | 99.0921 |
| 111.9949                 | C5H3CN+                           | 155.94438                     | C5H3BrN+                              | 155.9446 |
| 139.0059                 | C6H4CN2+                          | 182.95538                     | C6H4BrN2+                             | 182.9550 |
| 143.0816                 | C6H11N2O2+                        | 143.0816                      | C6H11N2O2+                            | 143.0815 |
| 217.1085                 | C11H13N4O+                        | 217.1085                      | C11H13N4O+                            | 217.1081 |
| 245.0226                 | C11H6CIN4O+                       | 288.97208                     | C11H6BrN4O+                           | 288.9713 |
| 247.0381                 | C11H8CIN4O+                       | 290.98758                     | C11H8BrN4O+                           | 290.9870 |
| 263.0332                 | C11H8CIN4O2+                      | 306.98268                     | C11H8BrN4O2+                          | 306.98201 |
| 277.0487                 | C12H10CIN4O2+                     | 320.99818                     | C12H10BrN4O2+                         | 320.9980 |
| 345.1227                 | C16H18CING6O+                     | 389.07218                     | C16H18BrN6O+                          | 389.0717 |
Observation of correlations of the 8.89 and 8.85 ppm signals as well as with the 8.52, 8.48 and 7.95 ppm signals in $^1$H-$^1$H COSY spectrum further confirmed these assignments (Figure 6). The isolated fraction tested positive in a commercial zopiclone/eszopiclone ELISA kit.

Discussion

Several studies performed over the last decade have shown intentional adulteration of natural health products and dietary supplements by the addition of pharmaceutical drugs [9–14]. Certain categories of products are often found to be adulterated, including products for weight loss, body building, erectile dysfunction, sleep problems, inflammatory conditions and metabolic disorders [8–13]. The complex matrices of these products can be analytically challenging for detection of the adulterants [13–15]. Further the use of analogs of those substances, with potentially unknown safety or pharmacological activity, not only makes detection very difficult, it renders the products themselves an unquantifiable public health risk [14, 15].

The reports of effects in consumers, not typically associated with the herbal ingredients listed on the U-Dream label, prompted an investigation that began with screening for known pharmaceutical drugs. The combination of the characteristic bromine isotope pattern observed in full scan accurate mass spectrum suggested the presence of a halogenated compound and prompted further investigations. From the MS/MS analysis of the 433 m/z product ion found in the U-Dream product it was observed the aligned fragmentation pattern (Table 4) of the unknown adulterant was consistent with a brominated analogue of the pharmaceutical sedative zopiclone.

To support the putative identification from the mass spectra studies, the compound was isolated and structure elucidated using $^1$H NMR. In Figure 5 we show the one-dimensional proton NMR of the unknown. A lack of resolution in the aliphatic region of the $^1$H NMR spectrum made assignment of the piperazinyl protons difficult and overall the intensity of the signals was lower than expected. These observations suggest that the fraction may have contained degradation products and impurities that were likely created over the course of storage.

Figure 5. $^1$H NMR spectrum of fraction obtained from suspected adulterated product.
of the isolation experiment. Despite the limitations in the proton NMR spectra obtained for the unknown, the correlations between the 8.89 and 8.85 ppm signals and the 8.52, 8.48, and 7.95 ppm signals in $^1$H-$^1$H COSY spectrum further confirmed the assignments. As depicted in Table 5, these assignments compared very well with signals for the published $^1$H NMR spectra of zopiclone [21]. Similar to the assignments proposed by Ming et al., (2007) the signals in this range, which were integrated for one proton each, were assigned to protons in the pyridyl and pyrazinyl rings. The assignment of the signals to the pyridyl protons were facilitated through the observed multiplet structure and coupling constants as depicted in Table 5.

The assignment of the unknown adulterant as a brominated analogue of zopiclone was further supported by the positive results from the commercial zopiclone/eszopiclone ELISA kit, indicating that the adulterant is likely biologically active. This finding is particularly concerning as the natural health product tested appears to have been adulterated with an undeclared compound having chemical similarities to a known prescription

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**Table 5.** Comparison of NMR data for the aromatic region reported for zopiclone and the analysis of the isolated fraction. Zopiclone chemical shifts were reported in Ming et al., 2007 [21]. Assignment numbers refer to the numbered atoms in Figure 3.

| $^1$H chemical shifts reported for zopiclone $\delta_H$ in ppm | $^1$H chemical shift observed for fractionated sample $\delta_H$ in ppm | Coupling constant $J$ (Hz) | Assignment | Multiplicity | $^1$H-$^1$H COSY $\delta_H$ in ppm |
|---------------------------------------------------------------|---------------------------------------------------------------|--------------------------|-------------|-------------|---------------------------------|
| 8.85                                                          | 8.89                                                          | 2.5                      | 15          | d           | 8.85                            |
| 8.81                                                          | 8.85                                                          | 2.5                      | 16          | d           | 8.89                            |
| 8.45                                                          | 8.50                                                          | 2.5                      | 12          | d           | 7.93                            |
| 8.32                                                          | 8.46                                                          | 8.9                      | 9           | d           | 7.93                            |
| 7.96                                                          | 8.01                                                          | 7                        |             | s           |                                 |
| 7.74                                                          | 7.93                                                          | 2.5, 8.9                 | 10          | dd          | 8.46, 8.50                       |

**Figure 6.** $^1$H-$^1$H COSY NMR spectrum of fraction obtained from suspected adulterated product.
pharmaceutical. It has been noted in the literature that synthesis of a chemically modified analogue of parent drug compounds, can be an effective means to avoid detection [15, 16].

Our study demonstrates that using a routine conventional drug screening method which targets specific pharmaceutical drugs, is not effective alone in identifying adulteration. The detection of the undeclared brominated analogue within this product required analysis of the mass spectrum followed by careful evaluation of its mass ion profile. Such a detailed analysis is not typically performed on a routine basis as only the targeted compounds are actively sought for and analysts would seldom have the time to check every single peak in a product that contains multiple herbal ingredients. Furthermore, because ELISA testing of the U-Dream product itself did not produce a positive result, the presence of herbal extracts in the product may have effectively masked the detection of the adulterant with ELISA test kits.

Zopiclone itself is an active pharmaceutical agent that while chemically unrelated to benzodiazepines, binds with high affinity to benzodiazepine receptors [22]. Cautionary statements to patients concerning zopiclone use include hepatic and renal impairment, history of drug use or psychiatric illness and contraindications include myasthenia gravis, respiratory failure, severe sleep apnoea syndrome, severe hepatic impairment, pregnancy and breast-feeding [23]. The most frequently reported adverse event, as cited in the 2006 WHO 34th Expert Committee on Drug Dependence, are bitter or metallic taste and dry mouth [23, 24]. Zopiclone, like many prescriptive sleeping medications, has the potential for abuse and addiction [25]. This risk is higher in patients with a prior history of drug/alcohol abuse or a history of psychiatric illness [26]. In addition, a small number of patients in many clinical trials of zopiclone developed rebound insomnia after discontinuing the drug [25].

Given this compound’s structural similarity to zopiclone and the testimonial reports describing adverse events consistent with those reported for zopiclone [18, 19, 23] it is likely the undeclared analogue has pharmacological activity. However this brominated analogue has not been subjected to pharmacological, toxicological or clinical investigations. “Designer drugs”, often referring to the manipulation of the chemical structure of known drugs such that resulting product is structurally similar but not identical, has been a growing concern worldwide [27–29]. Structural analogy with a known pharmaceutical is not alone sufficient to predict function or safety [27]. Although zopiclone is a prescription drug [30, 31], rather than an illegal psychoactive drug, as are often the targets of designer drugs, the suspected bromine analogue has no known safety profile and as such poses a substantial public health risk.

Conclusions
The NHP regulations provide a framework for high quality, safe and efficacious products to access the market in Canada. It is the responsibility of the manufacturer to assure traceability and transparency in their supply chain and establish verifiable compliance with GMP. The NHP U-Dream was suspected of containing an undeclared pharmaceutical based on testimonials of consumers. The experimental mass spectral data indicated the presence of an unknown bromine containing compound in the U-Dream product tested. Based on the fragmentation pattern the unknown was putatively identified as an analogue of zopiclone, whereby the chlorine atom had been substituted with bromine. This assignment was further corroborated by the NMR spectra and positive result from the commercial zopiclone/eszopiclone ELISA kit. The structural characteristics and consumer reviews of the product suggest that this undeclared, unknown compound has pharmacological activity, however to what extent is unknown. Of more considerable concern is the lack of any known safety profile by which to assess consumer risk. This study illustrates the importance of careful evaluation of analytical data in order to detect, not only undeclared adulterants, but unknown chemical entities and highlights the need for active monitoring and surveillance of potentially high-risk products post market entry.

List of Abbreviations
NHPs: natural health products
NNHPD: natural and non-prescription health products directorate
NPN: natural health product number
HPLC: high performance liquid chromatography
Q-ToF: quadrupole Time-of-Flight
MS/MS: tandem Time-of-Flight
H₂O: water
MeCN: acetonitrile
DAD: diode array detector
ESI: electro-spray ionization
NMR: nuclear magnetic resonance
COSY: correlation spectroscopy
CDCl₃: deuterated chloroform
ELISA: enzyme linked immunosorbent assay
HR-LCMS: high resolution liquid chromatography mass spectrometry
GMP: good manufacturing practice
Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

PNB: made contributions to the design of the study and substantial contributions to the data analysis and interpretation, drafted the manuscript including critically important intellectual content, gave final approval of the version to be published and as corresponding author agrees to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.  
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CC: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript, and gave final approval of the version to be published.

SK: made substantial contributions to the collection of data, drafting of protocols, and gave final approval for the version to be published.

YSR: made substantial contributions to the design, acquisition, analysis, and interpretation of data, drafting of protocol, and gave final approval for the version to be published.

JN-K: made contributions to the collection of data as well as interpretation and analysis of the data, revised the manuscript, made important intellectual contributions, and gave final approval of the version to be published.

MLH: made contributions to study design, the interpretation of the data, critically revised the manuscript, made important intellectual contributions, and gave final approval of the version to be published.

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