α-Glucosidase inhibitory activity of compounds isolated from the twig and leaf extracts of Desmos dumosus

Virayu Suthiphasilp a, Tharakorn Maneerat a, b, Raymond J. Andersen c, d, Brian O. Patrick d, Stephen G. Pyne e, Surat Laphookhieo a, b, *

a Center of Chemical Innovation for Sustainability (CIS), School of Science, Mae Fah Luang University, Chiang Rai 57100, Thailand
b Medicinal Plant Innovation Center of Mae Fah Luang University, Chiang Rai 57100, Thailand
c Department of Earth, Ocean & Atmospheric Sciences, University of British Columbia, 2036 Main Mall, V6T 1Z1 Vancouver, BC, Canada
d Department of Chemistry, University of British Columbia, 2036 Main Mall, V6T 1Z1 Vancouver, BC, Canada
e School of Chemistry and Molecular Bioscience, University of Wollongong, Wollongong, New South Wales, 2522, Australia

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ABSTRACT
Four new compounds, (+)-(2S)-desmosdumosone (1), (+)-(2R)-7,8-dimethoxy-5-hydroxylavonanone (7), (+)-(2R)-7-methoxychamanetin (9), and (+)-(1'R,2'R)-phebalosin (18), and 25 known compounds were isolated from the twig and leaf extracts of Desmos dumosus. Compounds (±)-7 and (±)-9 were isolated as racemates and their enantiomers were separated by chiral HPLC. Their structures were elucidated by spectroscopic methods as well as comparisons made from the literature. The absolute configuration of (+)-(1'R,2'R)-18 was established by X-ray diffraction analysis using Cu Kα radiation and electronic circular dichroism (ECD) spectroscopy. In contrast, the absolute configuration of compounds (+)-(2S)-1, (+)-(2R)-7, and (+)-(2R)-9 were identified by comparing their ECD spectra and specific rotations with those of reported known compounds. Compounds 9, 11, 13, 14, 22, 25, and 28 showed α-glucosidase inhibitory activities with IC₅₀ values ranging from 5.3-52.7 μM, much better than that of standard control (acarbose, IC₅₀ value 83.5 μM). Compound 13 was the most active with an IC₅₀ value of 5.3 μM.

1. Introduction

Diabetes mellitus (DM) accompanied by an increased blood glucose level is a metabolic disorder in which the pancreatic beta cells generate insufficient insulin [1]. Multiple complications can arise, including both macro and microvascular dysfunctions [2], where complete treatment with insulin and oral hypoglycemic agents without side effects is difficult [3]. In the recent literature, many phenolic compounds isolated from Annonaceae plants have been recommended to treat diabetes mellitus alone or in combination with hypoglycemic agents [4, 5].

Desmos dumosus (Roxb.) Saff. is a shrub belonging to the Annonaceae family and is distributed throughout Southeast Asia and Northern Australia [6]. The roots and leaves of this plant have been used in traditional medicines to treat malaria, inflammation, rheumatoid arthritis, roseola infantum rash, and dysentery in Chinese folk medicine [7, 8, 9, 10]. Previous phytochemical investigations of Desmos genus resulted in the isolation and identification of several types of compounds including, polyoxygenated flavonoids [7, 8, 9, 10, 11], cinnamylphenol [9, 12], artefact [11], aristolactam [13], aporphine [11, 13, 14], berberine [13, 14], orientalaline [11, 13], canadine [11, 13], isoquinoline [13, 14], morphinandienone alkaloids [14], benzoate ester [6], C-benzylated chalcone [10], sterol [13], hybrid flavan-chalcone [16], and oxepinone [17]. Some of these isolated compounds displayed a wide range of biological activities, including anti-HIV [12], anti-plasmodial [13], cytotoxicity [9, 13], antioxidant, aromatase and lipoxygenase inhibition [16], anti-fungal [18], and α-glucosidase [17], and tyrosine kinase inhibitory [19] activities. In this study, we report herein the isolation, structure elucidation, resolution, and absolute configuration assignments of three new flavonoids (1, 7, and 9) and one coumarin (18) together with 25 known compounds (2-29) from the twig and leaf extracts of D. dumosus, which were collected from Doi Tung, Chiang Rai.

* Corresponding author.
E-mail address: surat.lap@mfu.ac.th (S. Laphookhieo).
Province, Thailand. The crude extracts and some of isolated compounds were evaluated their α-glucosidase inhibitory activities.

2. Materials and methods

2.1. General experimental procedures

Melting points were measured on a Buchi melting point B-540 visual thermometer. The optical rotations were measured with a Bellingham and Stanley APD440 polarimeter. The UV spectra were recorded with a Perkin Elmer UV-Vis spectrophotometer. Infrared (IR) spectra were recorded using a Perkin Elmer Frontier Optica FT-IR spectrometer. Electronic circular dichroism spectra were recorded on a JASCO J-815 spectrometer. The NMR spectra recorded using 400 MHz Bruker AV-600 spectrophotometers. The HRESITOFMS were obtained on a Bruker microTOF mass spectrometer and Bruker-Hewlett-Packard 1100 Esquire-LC system mass spectrometer. The HREIMS were recorded using Kratos MS-50 mass spectrometer. Chiral HPLC was performed on a CHIRALPAKIA 15 column of 10–250 mm and attached to Waters 2487 Dual λ absorbance detector.

2.2. Plant material

The twigs and leaves of *D. dumosus* were collected from Doi Tung, Chiang Rai Province, Thailand in February 2016 (GPS coordinates: 20°17’30”N 99°48’30”E). The plant was identified by Mr. Matin Van de Bult (Doi Tung Development Project, Chiang Rai, Thailand). The specimen (MFU-NPR0110) was deposited at the Natural Products Research Laboratory, School of Science, Mae Fah Luang University.

2.3. Extraction and isolation

The fresh twigs of *D. dumosus* were dried at temperature (ca 27–35 °C, in summer season) for a week. Air-dried twigs of *D. dumosus* were extracted with EtOAc (20 L) for three days at room temperature. The crude extract (92.72 g) was subjected to QCC over silica gel using a gradient of hexanes and EtOAc (100% hexanes to 100% EtOAc) to afford 12 fractions (TF1–TF12). Fraction TF5 (7.70 g) was further fractionated by CC over Sephadex LH-20 (100% MeOH) to provide nine subfractions (LF1–LF9). Compound (4.7 mg) was further purified from subfraction LF7D4 (301.7 mg) by PTLC (1:10, v/v EtOAc/CH2Cl2) to provide 12 subfractions (TF9A–TF9L) and TF9I (271.7 mg) was isolated from subfraction TF9I (107.6 mg) by PTLC (1:10, v/v EtOAc/CH2Cl2).

2.3.1. (+)-(2S)-Desmosdusinone (1)

Yellow viscous oil, [α]D25 +16 (c 1.5, MeOH), UV (MeOH) λmax (log ε) 231 (2.07), 282 (2.04) and 341 (1.73) nm; IR (neat) νmax 2980, 2923, 2853, 1615, 1580, 1449, 1354, 1121, 1045, 787 and 678 cm−1; ECD (7.49 × 10−3 M, MeOH) λmax (Δε) 227 (+0.92), 242 (−0.45), 282 (−0.46), 297 (−0.26), 331 (+0.08) nm. 1H and 13C NMR data, see Table 1; HRESITOFMS m/z 299.0913 [M + H]+ (calcd for C17H16O5Na, 299.0919).

2.3.2. (±)-7,8-Dimethoxy-5-hydroxyflavone (7)

Colorless crystals, mp 158–159 °C, UV (MeOH) λmax (log ε) 215 (0.16), 290 (0.04), 345 (0.60) nm; IR (neat) νmax 3414, 1612, 1452, 1323, 1221 and 826 cm−1.

2.3.3. Resolution of compound 7 and ECD spectroscopic data of (−)-(2S)-7 and (+)-(2R)-7

Resolution of compound (−)-7 (4.3 mg) was performed by semi-preparative HPLC on a chiral column (CHIRALCEL OD-H, 4.6 × 250 mm, flow rate 1 mL/min, n-hexane/MeOH/PrOH, 70:20:10 v/v/v). Compounds (−)-(2S)-7 (tR 7.9 min) ([1.3 mg], [α]D 22 +23 (c 0.1, CHCl3)); ECD (1.0 × 10−3 M, MeOH) λmax (Δε) 225 (+1.27), 287 (−1.15), 331 (+0.60) nm.

Compounds (+)-(2R)-7 (tR 7.0 min) ([0.3 mg], [α]D 22 +31 (c 0.1, CHCl3)); ECD (1.0 × 10−3 M, MeOH) λmax (Δε) 225 (−1.19), 287 (+1.26), 331 (−0.54) nm; H and 13C NMR data, see Table 2; HRESITOFMS m/z 323.0898 [M + Na]+ (calcd for C17H12O5Na, 323.0895).

2.3.4. (±)-7-Methoxychamanetin (9)

Colorless viscous oil, UV (MeOH) λmax (log ε) 216 (0.03), 289 (0.37), 346 (1.21) nm; IR (neat) νmax 3452, 2937, 1636, 1497, 1313, 1100 and 1024 cm−1.
Figure 1. Isolation and purification diagram of D. dumosus twigs (Fr. TF5 and TF7).

Figure 2. Isolation and purification diagram of D. dumosus twigs (Fr. TF8 and TF9).
2.3.5. Resolution of compound 9 and ECD spectroscopic data of (−)-(2S)-9 and (+)-(2R)-9

Resolution of compound (−)-(2S)-9 (1.3 mg) was performed by semi-preparative HPLC on a chiral column (CHIRALCEL OD-H, 4.6 × 250 mm, flow rate 1 mL/min, n-hexane/iPrOH, 90:10 v/v).

| Position | δc (ppm) | δh (ppm) | J (Hz) |
|----------|----------|----------|--------|
| 2        | 101.3    |          |        |
| 3        | 48.4     | 3.09, s  |        |
| 4        | 194.8    |          |        |
| 4a       | 104.9    |          |        |
| 5        | 159.2    |          |        |
| 6        | 103.0    |          |        |
| 7        | 160.9    |          |        |
| 8        | 102.4    |          |        |
| 8a       | 154.2    |          |        |
| 6-CH3    | 8.0      | 2.11, s  |        |
| 8-CH3    | 7.0      | 2.16, s  |        |
| 1'       | 142.3    |          |        |
| 2'       | 125.1    | 7.73, d  | 7.0    |
| 3'       | 128.9    | 7.49, s  | 7.3    |
| 4'       | 129.3    | 7.47, d  | 7.1    |
| 5'       | 128.9    | 7.49, s  | 7.3    |
| 6'       | 125.1    | 7.73, d  | 7.0    |
| 5-OH     | 12.19    | 12.19, s |        |

Compound (−)-(2S)-9 (tR 7 min) [(0.5 mg), [α]D 23 71 (c 0.1, acetone)]; ECD (3.12 × 10⁻³ M, MeOH) λmax (Δε) 220 (+0.89), 287 (-0.90), 335 (+0.45) nm.

Compound (+)-(2R)-9 (tR 13 min) [(0.3 mg), [α]D 23 + 56.7 (c 0.1, acetone)]; ECD (3.12 × 10⁻³ M, MeOH) λmax (Δε) 220 (-0.86), 287 (+0.85), 335 (-0.34) nm; 1H and 13C NMR data, see Table 2; HREIMS m/z 399.1211 [M + Na]⁺ (calcd for C23H20O5Na, 399.1208).

2.4. X-ray crystallographic analysis of compounds (±)-7 and (+)-(2R)-9

Single colorless crystals of (+)-(2R)-9 (0.40 × 0.06 × 0.04 mm³) were selected and mounted on a mylar loop in oil on a Bruker APEX II area detector diffractometer. The structure was solved with the XT [20] structure solution program using the Intrinsic Phasing solution method and using Olex2 [21] as the graphical interface. The model was refined with version 2018/3 of XL [22] using Least Squares minimization.

X-Ray Crystallographic Data for (±)-7, 8-dimethoxy-5-hydroxylavone (C17H16O5), M = 300.30, monoclinic, space group P21/c, a = 5.16560 (10) Å, b = 25.7165 (7) Å, c = 10.6823 (3) Å, β = 90°, γ = 90°, V = 1418.96 (6) Å³, T = 90 (2) K, Z = 4. 

The x-ray diffraction analysis using Cu Kα radiation values was 0.862 cm⁻¹, 13976 reflections measured, 2483 unique (Rint = 0.0398) which were used in all
1.455 g/cm³. The x-ray diffraction analysis using Cu Kα radiation values for the specimen were 79.2, 5.48, dd (12.3, 3.2), 79.5, 5.52, dd (13.2, 2.9).

2.5. α-Glucosidase inhibitory activity

A colorimetric α-glucosidase assay was performed according to the previously described method [4, 5]. Briefly, the samples were dissolved in DMSO and further diluted with KH₂PO₄ buffer (c 100 mM, pH 6.8) to make the final concentration of 10% DMSO. The substrate, p-nitrophenyl α-D-glucoside (Sigma, St. Louis, USA; cat. no. N1377), was prepared in KH₂PO₄ buffer (c 1.5 mM). The mixture of 100 μL of enzyme solution (c 0.35 U/mL) and 50 μL of the isolated compounds was preincubated at 37 °C for 10 min. The enzymatic reaction was started by adding 100 μL of a substrate (c 1.5 mM), and the mixture was further incubated at 37 °C for 20 min. The enzyme activity was terminated by adding Na₂CO₃ (c 1 M, 1 mL), and the absorption at 405 nm was measured immediately. Acarbose was used as a positive control with an IC₅₀ value of 83.5 μM.

3. Results and discussion

3.1. Isolation and structure elucidation

The isolation and elucidation of EtOAc extracts of twigs and leaves from D. dumosus was purified by repeated chromatographic techniques to obtain fourteen flavonoids, a chalcone, two benzyl benzoates, two coumarins, eight aristolactam alkaloids, a seco-cyclohexene, and a cyclohexenes compounds (Figure 4) were identified to be 2,5,7-trihydroxy-8-formyl-6-methylflavanone (or desmal) (2) [19, 23], 2,5,7-trihydroxy-6-formyl-8-methylflavanone (3) [23] 5,7-dihydroxy-8-formyl-6-methylflavanone (or desmal) (4) [7], 5,7-dihydroxy-8-formyl-6-methylflavanone (5) [24], demethoxymetweeney (6) [24, 25], 7,8-dimethoxy-5-hydroxyflavanone (7) [45], 5-0-methylchamanetin (or chamanetin 5-Me ether) (8) [26], 7-methoxychamanetin (or 7-O-methylchamanetin) (9) [26, 48, 49], cryptochrysin (10) [27], 5,7-dihydroxy-6-methyl-8-formylflavone (11) [24], 5,7-dihydroxy-8-methyl-6-formylflavone (or isononual) (12) [24], matteuorien (13) [25], desmosdumotin B (or dasitrichon) (14) [28], desmosdumotin C (15) [29], benzyl benzoate (16) [30], 8-methoxycoumarin (17) [31], aristolactam BI (19) [32-36], 3,5-dihydroxy-2,4-dimethoxyaristolactam (20) [33], aristolactam BII (21) [32], 10-amino-3, 6-dihydroxy-2,4-dimethoxynaphthene-1-carboxylic acid lactam (22) [34], goniopedalin (23) [34], stigmalactam (24) [34], piperalactam D (25) [35], aristolactam I (26) [36], flexuvarin B (27) [37], cherrevelon A (28) [38], and benzoic acid (29) [39]. These structures were confirmed by comparisons of their spectroscopic and chemical properties with previously reported data.

Compound 1 was obtained from the twig extract as a yellow viscous oil. Its molecular formula was established as C₁₇H₁₅O₅, based on HRE-MS data. The x-ray diffraction analysis using Cu Kα radiation values was 3.866 cm⁻¹, 11560 reflections measured, 2762 unique (Rint = 0.0389) which were used in all calculations. The final wR₂ was 0.1267 (all data), R₂ = 0.0525 (I > 2σ(I)) and R₁ was 0.0534 (all data). The absolute configurations of compound (−)-18 was assigned as (R)R2R (Figure 8) with a Flack parameter was 0.072 (8). The crystallographic data of (−)-18 have been deposited in the Cambridge Crystallographic Data Centre as CCDC 2006686 and data can be obtained free of charge from the via http://www.ccdc.cam.ac.uk/data_request/cif.
Figure 4. Compounds isolated from twig and leaf extracts of D. dumosus.

Figure 5. COSY and selected HMBC correlations of compounds (+)-1, (+)-7, (+)-9, and (+)-18.
shift of the C-2 sp³ carbon (δC 101.3) indicated a hemiketal carbon of the flavanone core skeleton [42]. The full assignments of all ¹H and ¹³C NMR resonances, as well as HMBC correlations, were shown in Table 1. It should be noted that almost all of the naturally occurring absolute C-2 flavanone configurations containing the α-orientation 2-aryl substituent unit have been defined as (2S) [43, 44]. They will display a negative Cotton effect of the acetophenone chromophore transitions at 270–290 nm (π→π*) and a positive Cotton effect at 320–330 nm (n→π*) in ECD spectra [43, 44]. The ECD spectrum of 1 (Figure 6) showed positive Cotton effects at 227, 297, and 331 nm and negative Cotton effects at 242 and 282 nm similar to that of compound (–)–7, 8-dimethoxy-5-hydroxyflavanone (30), previously isolated from Zizyphus jujuba Mill. var. spinosa [44], which further supported the identification of the 2S absolute configuration of 1. Therefore, compound 1 was identified as (+)-(2R)-desmosdumosone.

The racemic mixture of (±)-7,8-dimethoxy-5-hydroxyflavanone (7), was first isolated from the root extracts of Andrographis paniculate in 1983 by Gupta and co-workers [45]. Then, in 1987, the S-configuration of (–)-7 was identified and isolated from Andrographis paniculate root extracts [46]. In our study, we isolated the racemic mixture of compound 7 as a colorless crystal. Its structure was confirmed by a single X-ray diffraction analysis using Cu Kα radiation (Figure 7, CCDC 2006685). Compound (±)-7 was resolved by semipreparative chiral HPLC to give compounds (–)–7 (tR 7 min), [α]D23 + 31 (c 0.1, CHCl₃) and (+)-7 (tR 7.5 min), [α]D23 + 31 (c 0.1, CHCl₃) in a ratio of ca 1:0.9 (Figure S28). The (2R) absolute configuration of (+)-7 was established by the comparison of its specific rotation and ECD spectrum with those of (–)-(2S)-7, 8-dimethoxy-5-hydroxyflavanone [46]. The ECD spectrum (Figure 6) of (2R)-7 [225 (–1.19), 287 (+1.26), 331 (–0.54) nm] was the mirror image of that of (2S)-7 [225 (+1.27), 287 (–1.15), 331 (+0.60) nm] and its specific rotation was also opposite sign ([α]D23 + 31.2 (c 0.1, CHCl₃) for (2R)-7 and [α]D23 – 23 (c 0.1, CHCl₃) for (2S)-7). Therefore, the new compound (+)-7 was identified as (+)-(2R)-7,8-dimethoxy-5-hydroxyflavanone. Detailed assignments of the protons and carbons as well as selected HMBC correlations are shown in Table 2 and Figure 5, respectively.

The racemic compound 9 (7-methoxychamanetin or 7-O-methylchamanetin) is a C-benzylated flavanone and was first isolated from the
root extract of *Xylopia africana* (Benth.) Oliver [47]. In 1976, William and co-workers [48] synthesized (-)-(2S)-7-methoxychamanetin, which had a specific rotation of $[\alpha]_D^{25} - 107.5$ (c 1.7, acetone) and its ECD spectrum displayed positive Cotton effects at 332 (c 860), 311 (c 1290), and 212 (c 3020) nm and negative Cotton effects at 287 (c 4320) and 235 (c 2520) nm. In this study, we resolved compound 9 by semi-preparative chiral HPLC to provide compound (-)-9 (ret 7 min), $[\alpha]_D^{25} - 71$ (c 0.1, CHCl3) and (+)-9 (ret 13 min), $[\alpha]_D^{25} + 57$ (c 0.1, CHCl3) in a ratio of ca 1:0.9 (Figure S28). The ECD spectrum (Figure 6) of (+)-9 [220 (-0.86), 287 (+0.85), 335 (-0.34) nm] was the mirror image of that of (-)-(2S)-7-methoxychamanetin ((-)-9) [48] indicating the absolute configuration of (+)-9 was opposite to that of 7-methoxychamanetin. Thus, compound (+)-9 was assigned as (+)-(2R)-7-methoxychamanetin. Full assignments of the protons and carbons as well as selected HMBC correlations are shown in Table 2 and Figure 5, respectively.

Phebalosin was first identified and isolated from *Phebalium tuberculatum* by Chow and co-workers in 1966 [49]. In 1989, Muhamad and co-workers isolated (-)-phebalosin ([$\alpha]_{20}^0 - 36$ (c 0.5, CHCl3)) from *Merrillia caloxylon* [50]. In this study, (+)-phebalosin (18) was isolated and its absolute configuration was identified from its specific rotation, ECD spectrum, and X-ray diffraction analysis. The NMR spectroscopic data (Table 3) were similar with (-)-phebalosin. The (1'R, 2'R) absolute configuration of (+)-phebalosin was established from X-ray crystallographic data analysis (Figure 8, CCDC 2006686) with the Flack parameter was showed to 0.072 (8). The ECD spectrum [213 (+2.01), 250 (-0.72), 270 (+0.68), 293 (-0.89), and 335 (+1.74) nm] is shown in Figure 9. Thus, compounds 18 was identified as (+)-(1'R, 2'R)-phebalosin as an enantiomer of (-)-phebalosin. Detailed assignments of the protons and carbons as well as selected HMBC correlations are shown in Table 3 and Figure 5, respectively.

### 3.2. $\alpha$-Glucosidase inhibitory activity of isolated compounds

Some isolated compounds (4, 7, 9–16, 19, 22, 25, and 28) were evaluated for their $\alpha$-glucosidase activities (Table 4). Compounds 9, 11, 13, 14, 22, 25, and 28 showed $\alpha$-glucosidase inhibitory activities with $IC_{50}$ values ranging from 5.3–52.7 $\mu$M, which were much better than that of standard control (acarbose, $IC_{50}$ value 83.5 $\mu$M). The $\alpha$-glucosidase inhibitory activities with $IC_{50}$ values of 120.9, 154.4, and 198.6 $\mu$M, respectively. Two remaining compounds (10 and 12) were shown to the inactive with $\alpha$-glucosidase inhibitory activity at 200 $\mu$g/mL.

### 4. Conclusions

The phytochemical investigations of *D. dumosus* collected from Doi Tung, Chiang Rai Province, Thailand led to the isolation and identification of four new compounds together with 25 known compounds. Most of flavanone previously isolated from Nature were reported to have the 2S configuration or were isolated as racemic mixtures [17, 51, 52, 53, 54]. In this study, (+)-(2R)-7,8-dimethoxy-5-hydroxyflavanone and...
Additional information

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Table 4. α-Glucosidase inhibitory activity of crude extract and isolated compounds from D. dumosus.

| Compounds       | α-Glucosidase inhibitory activity (IC50, μM) |
|-----------------|---------------------------------------------|
| 4               | 85.1                                        |
| 7               | 120.9                                       |
| 9               | 15.4                                        |
| 10              | inactive                                    |
| 11              | 36.0                                        |
| 12              | inactive                                    |
| 13              | 5.3                                         |
| 14              | 32.7                                        |
| 15              | 154.4                                       |
| 19              | 198.6                                       |
| 22              | 11.2                                        |
| 25              | 10.5                                        |
| 28              | 52.7                                        |
| Acarbose        | 83.5                                        |

(±)-(2R)-7-methoxysystematemin were obtained by the resolution of compounds (±)-7 and (±)-9, respectively, using semi-preparative chiral HPLC. The absolute configuration of all new compounds was established by comparing their ECD spectra with those of relevant reported compounds, except for compound (±)-(1R,2R)-18 which was determined using X-ray diffraction analysis (Cu Kα radiation). Compound 13 showed the most active α-glucosidase inhibitory activity (IC50 5.3 μM), much better than standard control (acarbose, IC50 value 83.5 μM). This compound may have the potential for further development as an anti-diabetic agent.

Declarations

Author contribution statement

Virayu Suthiphasilp: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Tharakorn Maneerat: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Raymond J. Andersen, Stephen G. Pyne: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Brian O. Patrick: Performed the experiments; Analyzed and interpreted the data.

Surat Laphookhieo: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.
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