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LC-MS guided isolation of *N*, β -glucopyranosyl vincosamide and other compounds from the curare ingredient *Strychnos peckii*

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Strychnos peckii (Loganiaceae) is an important active ingredient in curare poisons in the Amazon rainforest. Although previous studies have identified this species as a promising source of monoterpene indole alkaloids (MIAs), knowledge about other natural products is still scarce. Thus, to detect and guide the isolation of unprecedented bioactive compounds from the leaves of *S. peckii*, an untargeted high-performance liquid chromatography coupled with mass spectrometry (HPLC-MS) analysis was performed with the leaf aqueous extract. The HPLC-MS analysis allowed the detection of eleven compounds, including the alkaloids harman-3-carboxylic acid (**5**) and *N*, β -glucopyranosyl vincosamide (**6**), and the flavonoids quercetin 3-*O*-rhamnopyranoside (**9**) and kaempferol 3-*O*-rhamnopyranoside (**10**), all not previously reported in the Loganiaceae family. These compounds, along with strictosidine (**3**), 5-carboxystrictosidine (**7**), and desoxycordifoline (**8**) were isolated through modern chromatographic techniques and determined by using NMR spectroscopy in combination with MS. Overall, the untargeted HPLC-MS analysis proved to be a simple and effective approach to guide the isolation of substances not yet identified from *S. peckii*.

KEYWORDS

amazon rainforest, dereplication, flavonoid glycosides, monoterpene indole alkaloid, loganiaceae

1 Introduction

The genus *Strychnos*, the largest genus of the Loganiaceae family, comprises about 200 species distributed throughout South and Central America, Africa, Asia, Australia, and Polynesia (Ohiri et al., 1983; Adebowale et al., 2014; Guimarães et al., 2015). In Brazil, 68 species (28 endemics) are registered, 50 of which have been described in the North region (Guimarães et al., 2015). Although this genus has gained worldwide notoriety due to its importance in curare preparation (Philippe et al., 2004), several *Strychnos* species are used in traditional medicine to treat diarrhea, fever, malaria, syphilis, and other diseases (Basílio et al., 2005; Silva et al., 2005; Bonamin et al., 2011). In general, this broad spectrum of biological activities can be attributed to the presence of alkaloids (Quetin-Leclercq et al., 1990; Philippe et al., 2004; Tchinda et al., 2012)

and flavonoids (Nicoletti et al., 1984; Brasseur and Angenot, 1986). On the other hand, although many *Strychnos* species have been investigated from the phytochemical viewpoint, some species, especially those found in the Amazon region like *S. peckii*, still require complementary studies (Santos et al., 2019).

S. peckii B.L.Rob. is a liana species known worldwide as one of the active ingredients of curare (Philippe et al., 2004). Its distribution occurs in the North, Northeast, and Midwest regions of Brazil (Guimarães et al., 2015), but it is not an endemic species. A previous study based on strictosidine-derived alkaloids-targeted high-performance liquid chromatography coupled with mass spectrometry (HPLC-MS) analysis identified *S. peckii* as a promising source of monoterpene indole alkaloids (MIAs) (Santos et al., 2019), but no other phytochemical reports on this species are known. Recently, the application of modern analytical techniques, such as HPLC-MS, has been proven essential not only for the dereplication of alkaloids but also for the dereplication of phenolic compounds in plant extracts. (Paz et al., 2019; Silva et al., 2019; Lima et al., 2020). This mass spectrometry-based approach, typically relying on collision-induced dissociation (CID) fragmentation patterns, has demonstrated its effectiveness in identifying complex matrices and guiding the isolation steps of natural products (Paz et al., 2019; Lima et al., 2020). Thus, the aim of the present study was to detect and isolate unprecedented bioactive compounds from the leaf aqueous extract of *S. peckii* using untargeted HPLC-MS analysis. As a result, eleven compounds were detected, and seven of them were isolated, including the alkaloids harman-3-carboxylic acid (5) and *N*, β -glucopyranosyl vincosamide (6), as well as the flavonoids quercetin 3-*O*-rhamnopyranoside (9) and kaempferol 3-*O*-rhamnopyranoside (10).

2 Materials and methods

2.1 General experimental procedures

1D and 2D NMR experiments were acquired in a Bruker AVANCE III HD NMR spectrometer operating at 11.75 T (1H and 13C at 500 and 125 MHz, respectively). All ¹H and ¹³C NMR chemical shifts (δ) are presented in ppm relative to the tetramethylsilane (TMS) signal at 0.00 ppm as an internal reference, and the coupling constants (*J*) are given in Hz. HPLC-MS analysis was performed with an Accela HPLC system coupled to a TSQ Quantum Access (QqQ) mass spectrometer. The semi-preparative HPLC analysis was carried out on a Shimadzu UFLC system (LC-6 AD pump; DGU-20A5 degasser; SPD-20AV UV detector; rheodyne injector; CBM-20A communication module). All solvents used for chromatography and MS experiments were HPLC grade purchased from Tedia (Fairfield, OH, United States) and the water was purified by a Milli-Q system.

2.2 Plant material and extraction

Leaves from *S. peckii* were collected in May 2018 at the Adolpho Ducke Forest Reserve (SisGen registration number, AF4CFA7), Manaus, Amazonas State, Brazil (02° 55' 56.0" S, 059° 58' 16.0" W). The specimen, which was at the maturity stage, was identified at

the Herbarium of the National Institute of Research of Amazonia (INPA), where a voucher (number #282886) was deposited.

S. peckii leaves were immediately dried over ambient temperature (ca. 20°C) for 20 days (Resende et al., 2020), then powdered using an analytical knife micro-mill (80,374, Hamilton Beach, SP, Brazil). An aliquot of the powdered material (20 g) was extracted with distilled water (1,000 mL) by infusion (15 min) as previously described (Santos et al., 2019). The aqueous extract was filtered through Whatman 43 filter paper (Sigma-Aldrich) and then freeze-dried (Alpha 1-2 LDplus, Martin Christ, Germany), yielding the leaf aqueous extract (2.49 g, 12%).

2.3 HPLC-MS analysis

The leaf aqueous extract was diluted to 1 mg/mL in a water-methanol mixture (80:20, v/v) and analyzed (10 μ L, injection volume) with an HPLC-MS system equipped with an electrospray ionization (ESI) source. The HPLC was equipped with a Phenomenex Luna C18 (2) column (5 μ m, 150 mm \times 4.6 mm i.d.) (Torrance, CA, United States). The mobile phase consisted of water (A) and MeOH (B). The gradient elution was as follows: 0–15 min, 20%–80% B; 15–25 min, 80% B at a flow rate of 1.0 mL/min. The ESI source parameters were the following: spray voltage, 4500 V; sheath gas pressure, 35 arbitrary unit (arb); ion sweep gas pressure, 0.0 arb; aux gas pressure, 10 arb; capillary temperature, 230°C; tube lens offset, 109 V; skimmer offset, 0 V; mass range, *m/z* 100–1,000; collision energy, 35 eV.

2.4 Cleanup procedure and isolation

Before fractionation, an aliquot of the leaf aqueous extract (1 g) was subjected to a cleanup procedure, as previously described (Silva et al., 2019). Briefly, the sample was solubilized in 3 mL of distilled water and passed through a cartridge containing 10 g of C18 phase previously activated with methanol HPLC (100 mL) and conditioned with water (100 mL). The column was washed with water (100 mL) and further eluted with methanol HPLC (100 mL). The methanol phase was dried under a nitrogen gas stream, yielding the methanol fraction (0.63 g).

An aliquot of the methanol fraction (150 mg) was subjected to fractionation by semi-preparative HPLC using water (A) and methanol (B) as mobile phases. The gradient elution was as follows: 0–24 min, 20%–80% B (v:v), at a flow rate of 3.5 mL/min. A C18 column (250 mm \times 10 mm, 5 μ m) (Phenomenex—Torrance, CA, United States) was employed in the fractionation, monitored by UV channels at 280 and 316 nm. Five injections (30 mg each) were carried out into the column in a water-methanol mixture (80:20, v/v) (100 μ L), resulting in thirteen fractions (MF1–MF13). Fractions MF4 (3) (8.4 mg), MF8 (8) (19.9 mg), and MF10 (10) (10.9 mg) were subjected to NMR and MS analysis. The subfractions MF7.1 (5) (2.4 mg) and MF7.4 (7) (3.3 mg) were obtained from MF7 (19.4 mg), and MF9.2 (9) (2.0 mg) from MF9 (9.7 mg), which were individually subjected to fractionation by semi-preparative HPLC using the same mobile phase and C18 column. The gradient elution was as follows: 0–24 min, 30%–80% B (v:v), at a flow rate of 3.5 mL/min. The subfraction MF7.3 (3.2 mg) was further fractionated by semi-

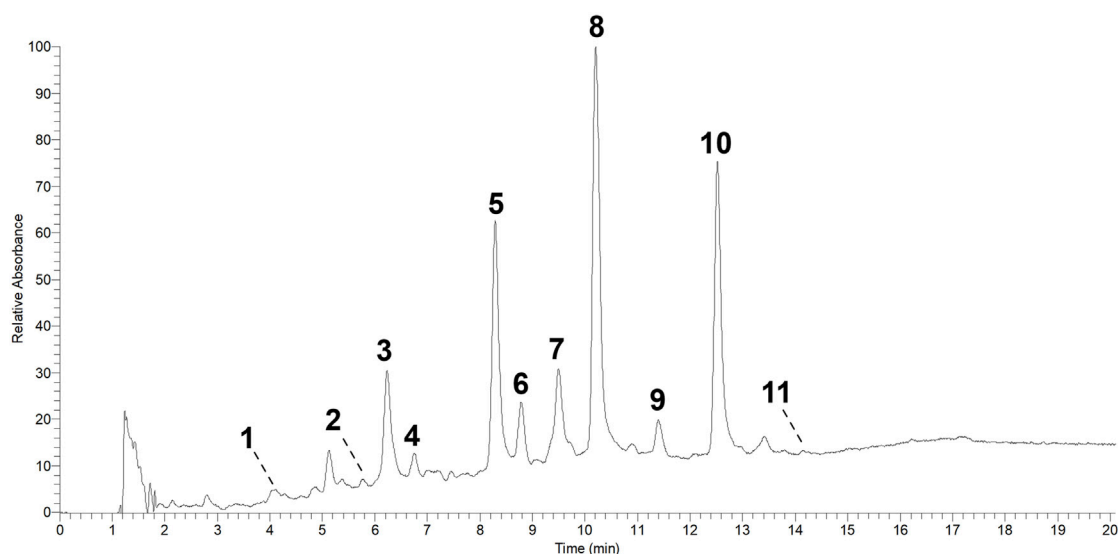


FIGURE 1
HPLC-MS total ion chromatogram (TIC) from the leaf aqueous extract of *S. peckii*.

TABLE 1 Alkaloids and flavonoids reported in *S. peckii* with their precursor ions and major fragments.

Compounds	R_t^a	$[M + H]^+$	$[M - H]^-$	MS/MS ^b
10-hydroxy strictosidine (1)	4.14	547	-	530, 368, 350
3,4-dehydro-strictosidine (2)	5.76	529	-	367, 349, 297, 265
strictosidine (3) ^c	6.23	531	-	514, 369, 352, 334, 320, 282
strictosidinic acid (4)	6.74	517	515	500, 355, 338, 320, 268
harman-3-carboxylic acid (5) ^c	8.29	227	225	199, 181, 154
<i>N</i> , β -glucopyranosyl vincosamide (6) ^c	8.79	661	-	499, 481, 429, 333
5-carboxystrictosidine (7) ^c	9.51	575	573	558, 413, 395, 396, 381, 343
desoxycordifoline (8) ^c	10.22	571	569	409, 391, 377, 339
quercetin 3- <i>O</i> - α -rhamnoside (9) ^c	11.42	449	447	303
kaempferol 3- <i>O</i> - α -rhamnoside (10) ^c	12.52	433	431	287
strictosidine lactam (11)	14.16	499	-	367, 337, 319

^aRetention time in minutes.

^bMain product ions obtained in QqQ-MS/MS, analyses in positive mode.

^cIsolated compounds.

preparative HPLC using a PFP column (250 mm \times 10 mm, 5 μ m) (Phenomenex—Torrance, CA, United States) with a gradient elution as follows: 0–24 min, 30%–80% B (v:v), affording MF7.3.2 (6) (2.0 mg).

3 Results and discussions

The HPLC-MS total ion chromatogram (TIC) of the leaf aqueous extract (Figure 1) showed the presence of at least 7 major compounds (3, 5, 6, 7, 8, 9, and 10) and 4 minor compounds (1, 2, 4, and 11). Thus, all these compounds were subjected to HPLC-MS/MS analysis.

The MS/MS spectra of the major compounds 3 (m/z 531), 7 (m/z 575), and 8 (m/z 571) displayed fragmentation patterns (Table 1) that are in agreement with the MIAs strictosidine (3), 5-carboxystrictosidine (7), and desoxycordifoline (8) (Figure 2), all previously reported from *S. peckii* (Santos et al., 2019). Also, the MS/MS spectra of the compounds 1 (m/z 547), 2 (m/z 529), 4 (m/z 517), and 11 (m/z 499) are in accordance with the MIAs 10-hydroxy strictosidine (1), 3,4-dehydro-strictosidine (2), strictosidinic acid (4), and strictosidine lactam (11) (Santos et al., 2019).

Moreover, the MS/MS spectrum of the compound 6 (m/z 661) showed a high spectral similarity with strictosidine lactam (11) (-162 Da, m/z 661 \rightarrow m/z 499; -18 Da, m/z 499 \rightarrow m/z 481;

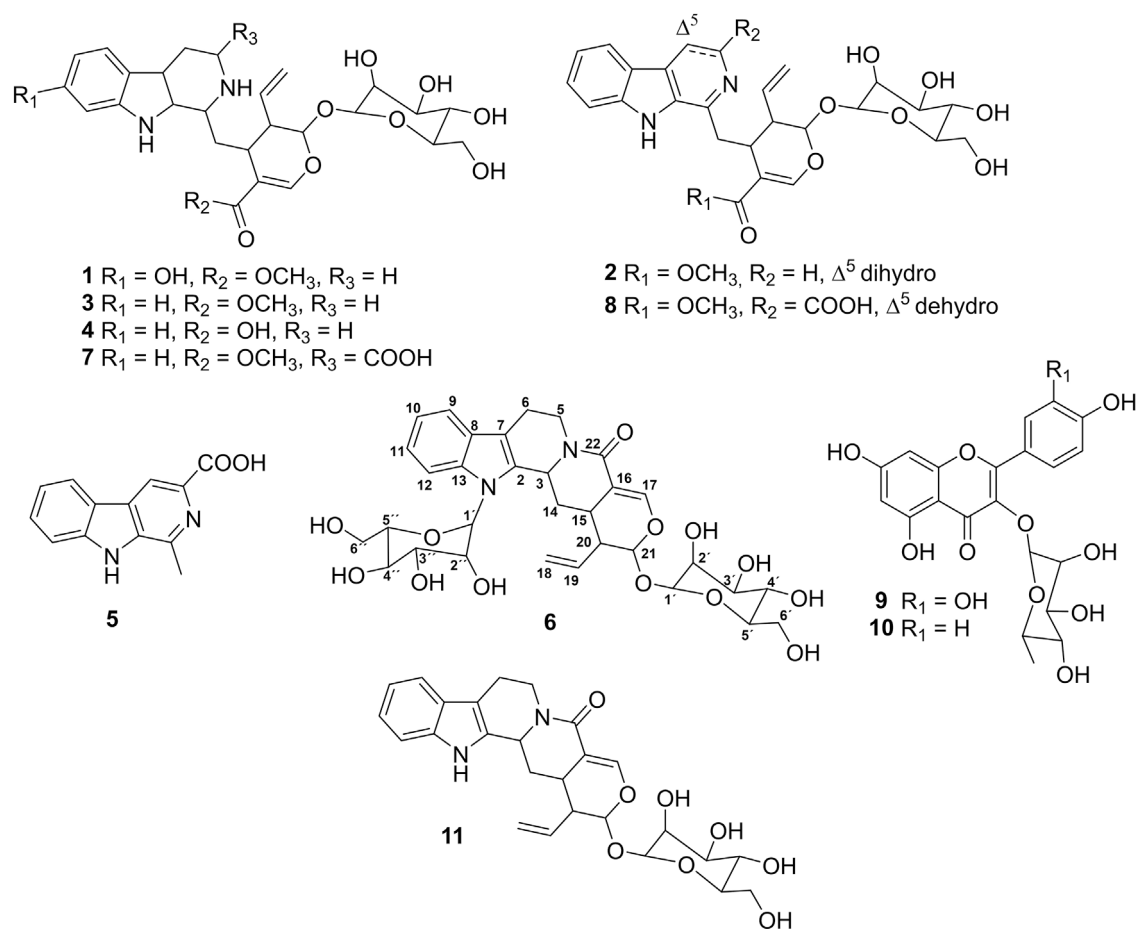


FIGURE 2

Chemical structures of alkaloids and flavonoids from the leaves of *S. peckii*.

–70 Da, m/z 499 \rightarrow m/z 429), suggesting that these compounds differ by an additional sugar unit. Since the initial sugar loss did not affect the other competitive losses of 18 and 70 Da, also observed to **11**, its glycosylation position was supposed to be at the tetrahydroharman moiety. To the best of our knowledge, there are no structures previously described in the Loganiaceae family with these characteristics. On the other hand, the MS/MS spectrum of the compound **5** (m/z 227) showed subsequent losses of CO (–28 Da, m/z 227 \rightarrow m/z 199) and H₂O (–18 Da, m/z 199 \rightarrow m/z 181), also incompatible with any compound previously reported from the Loganiaceae family. Moreover, the MS/MS spectra of the compound **9** (m/z 449) and **10** (m/z 433) showed losses of 146 Da (m/z 449 \rightarrow m/z 303; m/z 433 \rightarrow m/z 287), suggesting the presence of rhamnoside derivatives in the sample (March et al., 2004), also not previously reported in Loganiaceae family. Thus, these compounds along with other majority compounds were isolated for further structural confirmation by 1D and 2D NMR analysis.

The compound **6** was isolated as an amorphous solid. As previously discussed, the mass spectra pointed this compound as a strictosidine lactam derivative containing a glucose unit in the tetrahydroharman moiety. Therefore, its structural confirmation was based mainly in key correlations for characteristic signals at this moiety. Several diagnostic signals for tetrahydroharman moiety were observed in the ¹H NMR spectrum (Table 2), among them, aromatic protons at δ_H 7.52 (1H, d, $J =$

8.3 Hz, H-12), 7.47 (1H, d, $J = 7.8$ Hz, H-9), 7.10 (m, H-11), and 7.05 (m, H-10), confirming the absence of replacement in ring A. According to the HMBC spectrum, H-11 showed correlation with carbons C-13 (δ_C 135.0) and C-9 (δ_C 117.8). Also, the anomeric hydrogen H-1'' [δ_H 5.06 (1H, d, $J = 9.3$ Hz)] showed correlations with C-13 (δ_C 135.0), which confirmed the *N*-substitution. The anomeric configuration was attributed as β through the characteristic chemical shift and large coupling constant (Gurst, 1991; Henriques et al., 2004). Thus, through the comparison of NMR data (Table 1) with the literature (Zhang et al., 2001; Henriques et al., 2004), compound **6** was identified as *N*- β -glucopyranosyl vincosamide. To the best of our knowledge this compound is being reported in Loganiaceae family for the first time. Regarding the biological activities of *N*- β -glucopyranosyl vincosamide, only one study describing its antioxidant potential has been previously reported (Matsuura and Fett-Neto, 2013). In this study, *N*- β -glucopyranosyl vincosamide demonstrated significant hydrogen peroxide quenching activity *in situ*. Additionally, *in vitro* antioxidant tests have also shown efficient quenching activity for this alkaloid. (Matsuura and Fett-Neto, 2013).

The other compounds were identified by analysis NMR and MS data and comparison with literature as strictosidine (**3**) (Patthy-Lukáts et al., 1997), harman-3-carboxylic acid (**5**) (Pereira et al., 2006), 5-carboxystrictosidine (**7**) (Rakumitsu et al., 2019), desoxycordifoline (**8**) (Brandt et al., 1999), quercetin 3-*O*- α -

TABLE 2 Assignment of ^1H and ^{13}C NMR data for the *N*, β -D-glucopyranosyl vincosamide (6).

Position	<i>N</i> , β -glucopyranosyl vincosamide (6)		HMBC ^c
	^1H δ (mult., <i>J</i> in Hz) ^a	^{13}C ^b	
2	-	134.6	-
3	4.54 (m)	50.1	-
5	2.67 (m) and 4.66 (m)	38.8	50.1, 109.8
6	2.63 (m) and 2.80 (m)	20.0	-
7	-	109.8	-
8	-	127.2	-
9	7.47 (<i>d</i> , 7.8)	117.8	121.3, 135.0
10	7.05 (m)	119.4	113.7, 127.2
11	7.10 (m)	121.3	117.8, 135.0
12	7.52 (<i>d</i> , 8.3)	113.7	119.4, 127.2
13	-	135.0	-
14	1.81 (m) and 2.73 (m)	32.3	-
15	3.16 (m)	23.0	-
16	-	108.7	-
17	7.10 (m)	146.0	108.7
18	5.55 (m) and 5.43 (m)	121.1	44.1
19	5.91 (m)	133.5	-
20	2.50 (m)	44.1	-
21	5.35 (s)	94.7	23.0, 97.5, 146.0
1'	4.52 (m)	97.5	94.7
2'	2.98 (m)	72.9	-
3'	3.34 (m)	77.4	-
4'	3.04 (m)	69.8	-
5'	3.15 (m)	76.6	-
6'	3.69 (m) and 3.41 (m)	60.8	-
1''	5.06 (<i>d</i> , 9.3)	85.0	70.5, 135.0
2''	4.25 (m)	70.5	-
3''	3.29 (m)	79.4	-
4''	3.32 (m)	69.7	-
5''	3.29 (m)	79.4	-
6''	3.69 (m) and 3.41 (m)	60.8	-

^aDMSO-*d*₆, 500 MHz.^bProtonated carbons assigned using an HSQC, experiment and quaternary carbons assigned using the HMBC, experiment.^cMost significant correlations observed in HMBC.

rhamnopyranoside (9) (Yuk et al., 2018), and kaempferol 3-*O*-rhamnopyranoside (10) (Yuk et al., 2018). To the best of our knowledge, the harman-3-carboxylic acid (5), quercetin 3-*O*-

rhamnopyranoside (9), and kaempferol 3-*O*-rhamnopyranoside (10) are also reported in Loganiaceae family for the first time.

Similarly to *N*- β -glucopyranosyl vincosamide (6), the MIAs 3,4-dehydro-strictosidine (2), strictosidine (3), strictosidinic acid (4), harman-3-carboxylic acid (5), 5-carboxystrictosidine (7), and desoxycordifoline (8) have also been previously reported to exhibit significant antioxidant potential (Cardoso et al., 2004). In the same study, desoxycordifoline (8), reported here as the major compound of the leaf aqueous extract, exhibited significant acetylcholinesterase activity. On the other hand, the flavonoids quercetin 3-*O*-rhamnopyranoside (9) and kaempferol 3-*O*-rhamnopyranoside (10) have also demonstrated efficient antioxidant potential (Babujanathanam et al., 2011; Akter et al., 2022). Moreover, kaempferol 3-*O*-rhamnopyranoside (10), the second major compound in the leaf aqueous extract, has been identified as a potential therapeutic agent in preventing oxidative stress-induced damage in melanocytes and other biomolecules. It has also been suggested for therapeutic use in chemotherapy and the treatment of vitiligo (Jung et al., 2017; Akter et al., 2022). Additionally, kaempferol 3-*O*-rhamnopyranoside (10) has shown potential for preventing PM-induced inflammatory skin diseases (Kim et al., 2019).

4 Conclusion

In conclusion, this study demonstrates that untargeted HPLC-MS analysis was a promising approach for identifying unprecedented bioactive compounds in *S. peckii*. The analysis revealed the presence of eleven compounds, including harman-3-carboxylic acid (5), *N*, β -glucopyranosyl vincosamide (6), quercetin 3-*O*-rhamnopyranoside (9), and kaempferol 3-*O*-rhamnopyranoside (10), which have not been reported in the Loganiaceae family. Along with other three MIAs, these compounds were successfully isolated using modern chromatographic techniques and identified through NMR spectroscopy in combination with MS. Overall, our study highlights the potential of untargeted HPLC-MS analysis as a simple and effective tool for guiding the isolation of unprecedented bioactive compounds from *S. peckii*.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

Conceived and designed the experiments: CS, MP, and FS. Performed the experiments: CS, KN, FS-F, and BL; analyzed the data: CS, EC, AS, HK, MP, and FS. writing—original draft: CS, HK, and FS. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors HK, FS, and EC declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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