### Supplementary Information for

# Pharmacokinetics and metabolism of cinnamic acid derivatives and flavonoids after oral administration of Brazilian green propolis in human

Masayuki Yamaga <sup>a,b\*</sup>, Hiroko Tani <sup>a</sup>, Miyu Nishikawa <sup>c</sup>, Keisuke Fukaya <sup>c</sup>, Shin-ichi Ikushiro <sup>c</sup>, Kaeko Murota <sup>b,d \*</sup>

<sup>a</sup> Institute for Bee Products and Health Science, Yamada Bee Company Inc., 194 Ichiba, Kagamino-cho, Tamata-gun, Okayama, 708-0393, Japan.

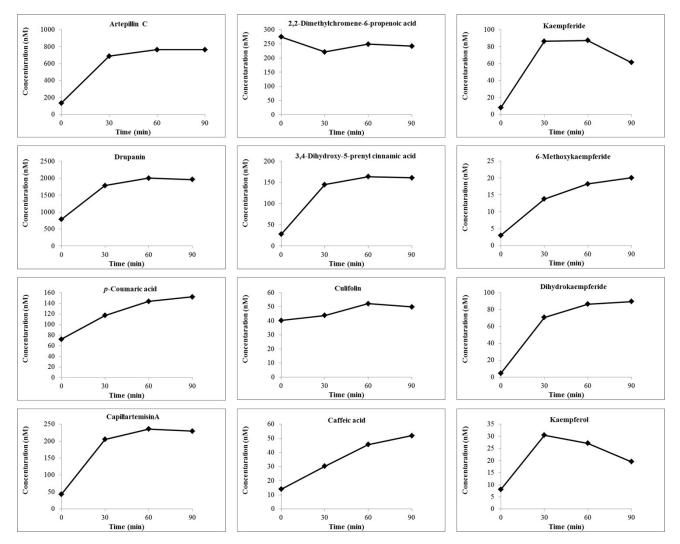
<sup>b</sup> Applied Bioresource Chemistry, Bioresource & Life Science, The United Graduate School of Agricultural Science, Tottori University, 4-101 Koyama-cho Minami, Tottori, Tottori, 680-8550, Japan.

<sup>c</sup> Department of Biotechnology, Faculty of Engineering, Toyama Prefectural University, 5180 Kurokawa, Imizu, Toyama, 939-0351, Japan.

<sup>d</sup> Department of Life Sciences, Faculty of Life and Environment Life Sciences, Shimane University, 1060 Nishikawatsu-cho, Mastue, Shimane, 690-8504, Japan.

#### **Table of contents**

- Figure S1. Time courses of plasma concentration of each composition during enzymatic hydrolysis reaction.
- Chemical shifts of artepillin C-4-O-β-D-glucuronide and drupanin 4-O-β-D-glucuronide
- Figure S2. <sup>1</sup>H NMR spectrum of artepillin C-4-*O*-β-D-glucuronide
- Figure S3. <sup>13</sup>C NMR spectrum of artepillin C-4-*O*-β-D-glucuronide
- Figure S4. HMBC spectrum of artepillin C-4-*O*-β-D-glucuronide
- Figure S5. <sup>1</sup>H NMR spectrum of drupanin 4-*O*-β-D-glucuronide
- Figure S6. <sup>13</sup>C NMR spectrum of drupanin 4-*O*-β-D-glucuronide
- Figure S7. HMBC spectrum of drupanin 4-O-β-D-glucuronide



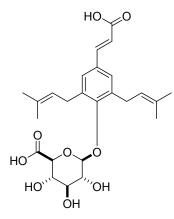
**Figure S1.** Time courses of plasma concentration of each composition during enzymatic hydrolysis reaction. The plasma sample collected from a volunteer at 1h after BGP intake was mixed deconjugation enzyme and incubated at 37 °C. After incubation at 0 (Immediately after the addition of enzyme), 30, 60, and 90 min, methanol was added to stop the reaction. These samples were prepared to LC/MS/MS analysis according to methods section.

#### Chemical shifts of artepillin C-4-O-β-D-glucuronide and drupanin 4-O-β-D-glucuronide

#### General Details

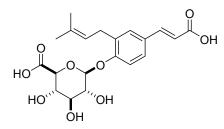
All NMR spectra were recorded on Bruker AVANCE NEO 500 spectrometer. Chemical shifts are reported in ppm on the  $\delta$  scale relative to CD<sub>2</sub>HOD ( $\delta$  = 3.31 for <sup>1</sup>H NMR), CD<sub>3</sub>OD ( $\delta$  = 49.0 for <sup>13</sup>C NMR) as internal references. Signal patterns are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broaden peak).

artepillin C-4-O-B-D-glucuronide



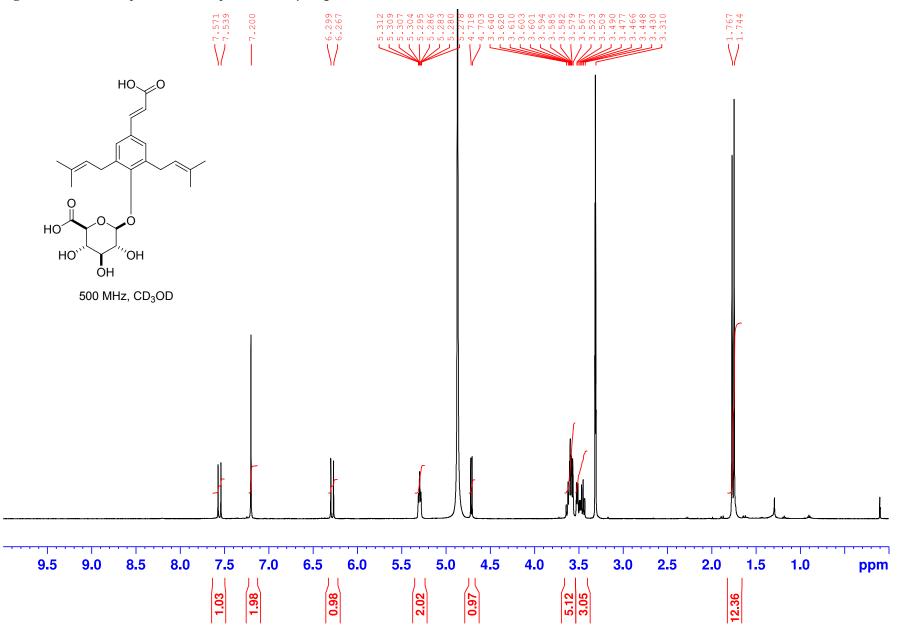
<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  1.74 (6H, s), 1.77 (6H, s), 3.42–3.54 (3H, m), 3.54–3.65 (5H, m), 4.71 (1H, d, J = 7.8 Hz), 5.27–5.32 (2H, m), 6.28 (1H, d, J = 15.9 Hz), 7.20 (2H, s), 7.55 (1H, d, J = 15.9 Hz). <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD)  $\delta$  18.1, 25.9, 29.6, 73.3, 75.4, 77.2, 77.5, 106.1, 118.2, 124.1, 128.5, 132.2, 133.8, 137.5, 146.2, 155.7, 170.7, 173.1.

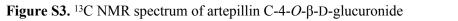
drupanin 4-O-β-D-glucuronide

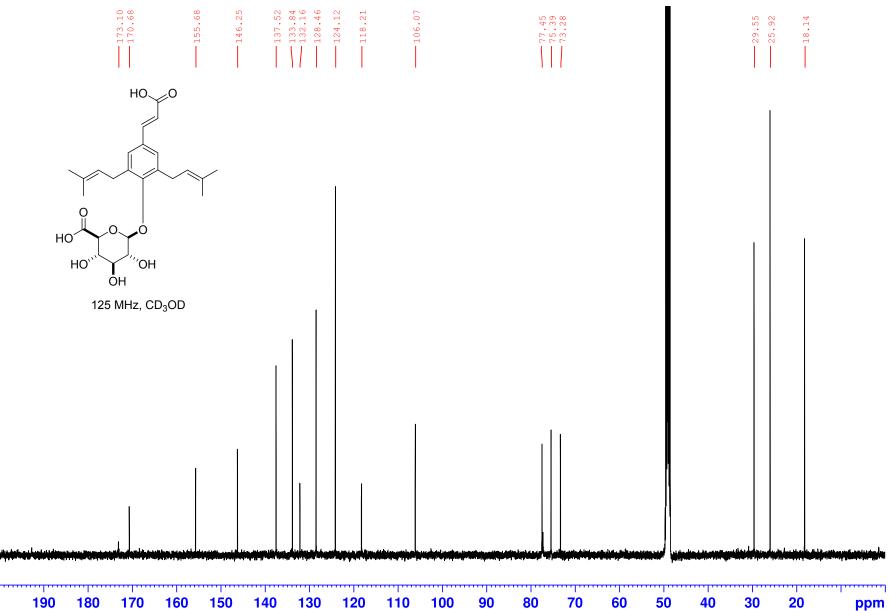


<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  1.74 (3H, s), 1.76 (3H, s), 3.40 (1H, dd, J = 15.7, 7.3 Hz), 3.45 (1H, dd, J = 15.7, 7.3 Hz), 3.51 (1H, dd, J = 9.1, 9.0), 3.56 (1H, dd, J = 9.0, 7.5), 3.63 (1H, dd, J = 9.7, 9.1), 3.99 (1H, d, J = 9.7 Hz), 5.04 (1H, d, J = 7.5 Hz), 5.33–5.38 (1H, m), 6.32 (1H, d, J = 15.9 Hz), 7.12 (1H, d, J = 8.5 Hz), 7.35 (1H, d, J = 2.0 Hz), 7.41 (1H, d, J = 8.5, 2.0 Hz), 7.60 (1H, d, J = 15.9 Hz). <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD)  $\delta$  17.9, 25.9, 29.2, 72.9, 74.7, 76.6, 77.6, 102.4, 116.4, 117.3, 123.3, 128.4, 130.1, 130.3, 133.3, 133.9, 146.2, 158.4, 170.7, 172.3.

Figure S2. <sup>1</sup>H NMR spectrum of artepillin C-4-*O*-β-D-glucuronide







## **Figure S4.** HMBC spectrum of artepillin C-4-O-β-D-glucuronide

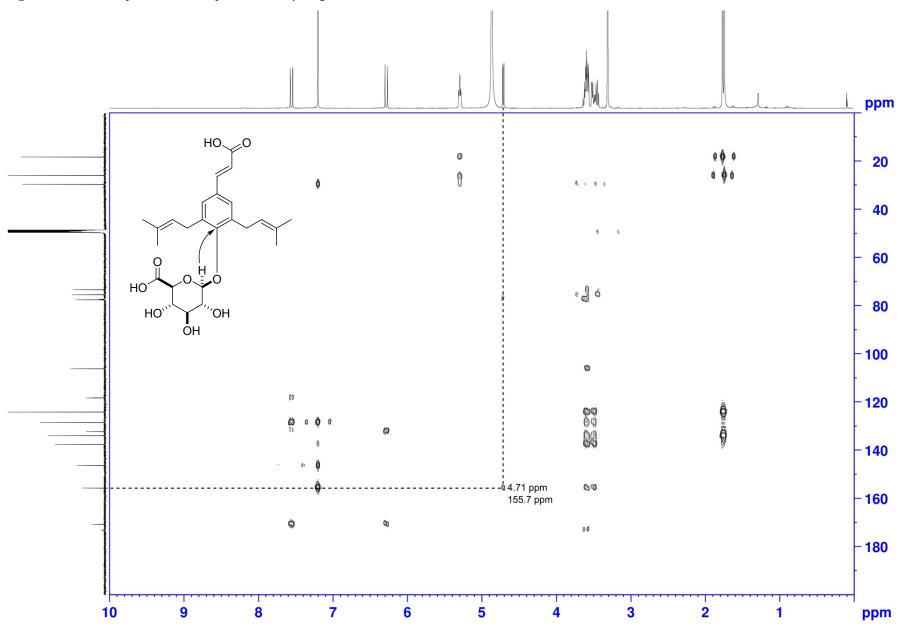
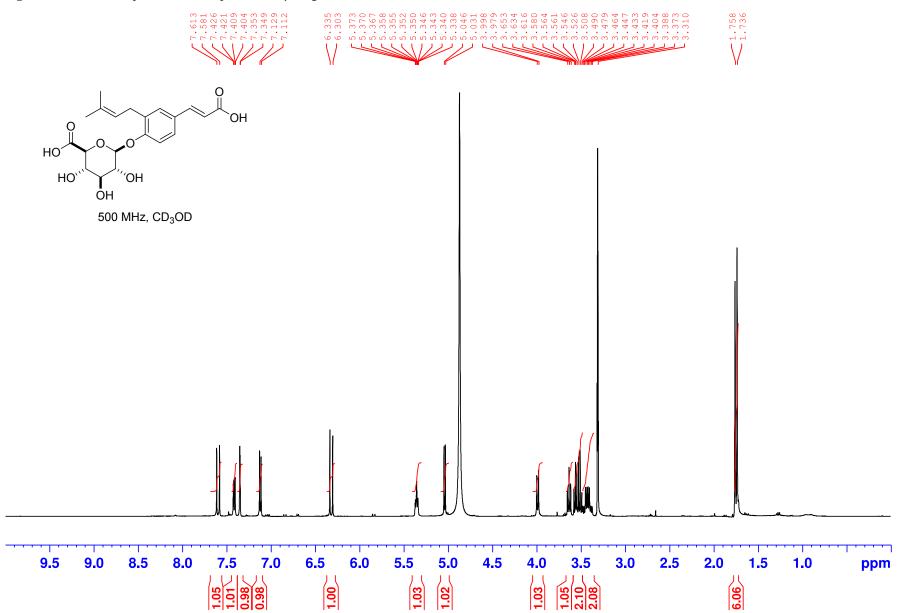
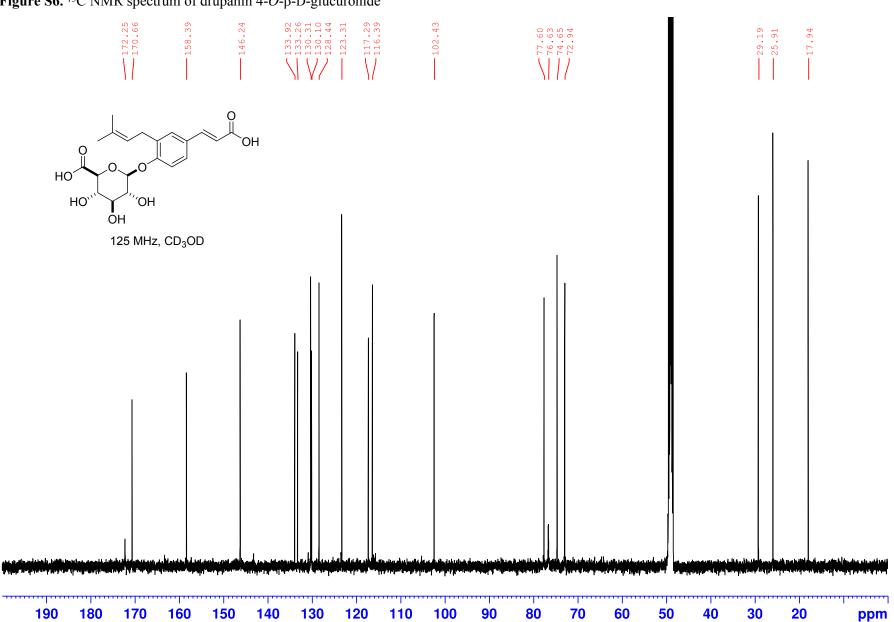


Figure S5. <sup>1</sup>H NMR spectrum of drupanin 4-O-β-D-glucuronide





**Figure S6.** <sup>13</sup>C NMR spectrum of drupanin 4-*O*-β-D-glucuronide

