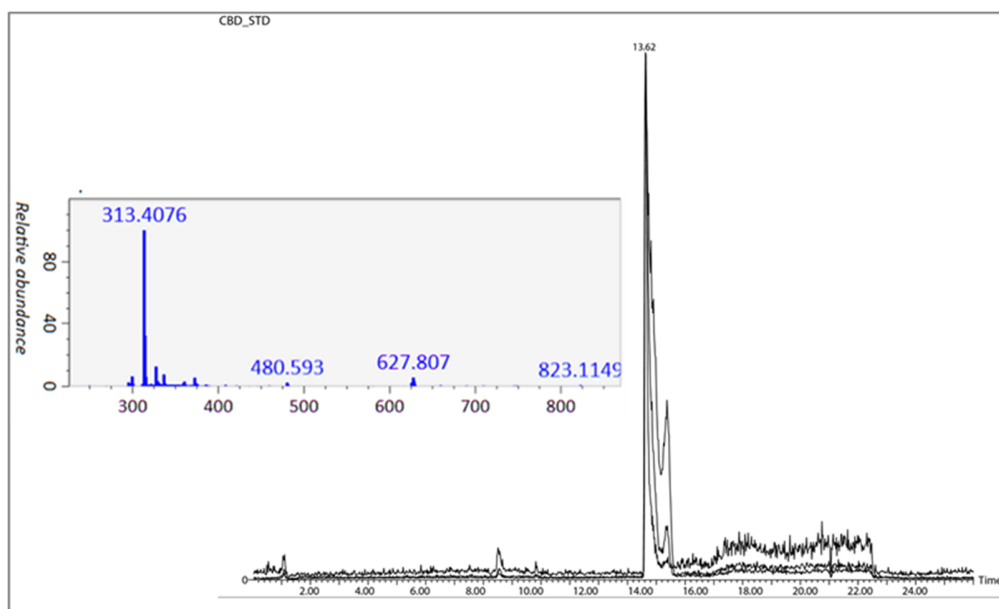


## Supplementary data

**Table S1.** *In-vitro* human digestion reagents and solutions

|                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Gastric and Small Intestinal Phase Solutions</b> | <p>Pepsin Solution (2mL per reaction)<br/>10 mg/mL Pepsin in 0.1M HCl</p> <p>Pancreatin-Lipase Solution (2mL per reaction)<br/>20 mg/mL Pancreatin (in 100mM NaHCO<sub>3</sub>)<br/>10 mg/mL Lipase (in 100mM NaHCO<sub>3</sub>)<br/>1.5 mg/mL Colipase (in 100mM NaHCO<sub>3</sub>)</p> <p>Bile Solution (3mL per reaction)<br/>30 mg/mL Bile Extract (in 100mM NaHCO<sub>3</sub>)</p>                                                                                                                                                   |
| <b>Preparation of Oral Phase</b>                    | <p>Base Solution (q.s. to 1 L with DI water):</p> <p>Potassium Chloride 1.792g<br/>Sodium Phosphate 1.776g<br/>Sodium Sulfate 1.140g<br/>Sodium Chloride 0.596g<br/>Sodium Bicarbonate 3.388g</p>                                                                                                                                                                                                                                                                                                                                         |
| <b>For ~10 g Porridge/100mL Oral Phase Solution</b> | <ol style="list-style-type: none"> <li>1. Add 100 mL base solution to beaker with stir bar</li> <li>2. Add 40 mg urea</li> <li>3. Add 3 mg uric acid</li> <li>4. Add 5 mg mucin per mL base solution – Note: For 100mL base solution add 500mg.</li> <li>5. Add 3.18 g <math>\alpha</math>-amylase</li> <li>6. Add other enzymes mentioned below right before digestion</li> <li>7. Mix well (at least 15 minutes)</li> </ol>                                                                                                             |
| <b>Enzymes for 100mL Base Solution</b>              | <p><math>\alpha</math>-amylase –Sigma, A3176. The activity is 15.8 units/mg of solid at pH 6.9 of food to be digested<br/>(15.8 units/mg) <math>\times</math> (31.8 mg/ml) <math>\times</math> (6ml) = 3015 units per digestion</p> <p><math>\beta</math>-glucosidase –0.05mg<br/><math>\beta</math>-galactosidase – 0.0034 mg<br/><math>\beta</math>-glucuronidase – 0.0008 mg<br/>Sulfatase – 0.0065 mg<br/>Phosphatase alkaline – 0.25 mg<br/>Phosphatase acid – 0.185 mg<br/>Neuraminidase – 0.0000024 mg<br/>Lysozyme – 0.108 mg</p> |



**Figure S1.** Chromatograms with the mass spectrum of standards obtained from UPLC- QTOF-MS analysis of standards of CBD at 13.62 retention time and m/z 313.4076 in negative mode. The chromatograms were analyzed using the MS-DIAL ver. 4.18.  $[M-H]^-$

**Table S2.** Inclusion list of metabolites for the CBD with the expected metabolites.

| Masses   | Names      |
|----------|------------|
| 314.4605 | CBD        |
| 330.4611 | 7-OH CBD   |
| 344.4446 | 7-COOH CBD |

**Table S3.** ANOVA analysis of variance using Tukey's Studentized Range (HSD) Test with SAS University Edition for comparison of the %mole conversion of pNPP to NP with and without bile experiment.

| Comparisons significant at the 0.05 level are indicated by ***. |                          |                                    |         |  |
|-----------------------------------------------------------------|--------------------------|------------------------------------|---------|--|
| Group Comparison                                                | Difference Between Means | Simultaneous 95% Confidence Limits |         |  |
| 0.1 mM pNPP – 1mM pNPP                                          | 0.44979                  | -0.17364                           | 1.07323 |  |
| 1 mM pNPP – 0.1 mM pNPP                                         | -0.44979                 | -1.07323                           | 0.17364 |  |

**Table S4.** ANOVA analysis of variance using Tukey's Studentized Range (HSD) Test with SAS University Edition for comparison of the AQ and DG phases of digestion in both fed and starved digestion experiments.

***Tukey's Studentized Range (HSD) Test for Fasted Digestion Percent Recoveries***

| Comparisons significant at the 0.05 level are indicated by ***. |                          |                                    |         |     |
|-----------------------------------------------------------------|--------------------------|------------------------------------|---------|-----|
| Group Comparison                                                | Difference Between Means | Simultaneous 95% Confidence Limits |         |     |
| DG100mg - DG10mg                                                | 18.288                   | 58.658                             | 24.365  | *** |
| DG100mg - AQ10mg                                                | 92.890                   | 79.561                             | 106.219 | *** |
| DG100mg - AQ100mg                                               | 93.475                   | 80.146                             | 106.804 | *** |
| DG10mg - DG100mg                                                | -18.288                  | -31.617                            | -4.959  | *** |
| DG10mg - AQ10mg                                                 | 74.602                   | 61.273                             | 87.931  | *** |
| DG10mg - AQ100mg                                                | 75.187                   | 61.857                             | 88.516  | *** |
| AQ10mg - DG100mg                                                | -92.890                  | -106.219                           | -79.561 | *** |
| AQ10mg - DG10mg                                                 | -74.602                  | -87.931                            | -61.273 | *** |
| AQ10mg - AQ100mg                                                | 0.585                    | -12.744                            | 13.914  |     |
| AQ100mg - DG100mg                                               | -93.475                  | -106.804                           | -80.146 | *** |
| AQ100mg - DG10mg                                                | -75.187                  | -88.516                            | -61.857 | *** |
| AQ100mg - AQ10mg                                                | -0.585                   | -13.914                            | 12.744  |     |

*Tukey's Studentized Range (HSD) Test for Fed Digestion Percent Recoveries*

Comparisons significant at the 0.05 level are indicated by \*\*\*.

| Group Comparison  | Difference Between Means | Simultaneous 95% Confidence Limits |         |     |
|-------------------|--------------------------|------------------------------------|---------|-----|
| DG10mg - DG100mg  | 3.109                    | -17.406                            | 23.624  |     |
| DG10mg - AQ100mg  | 67.605                   | 47.090                             | 88.120  | *** |
| DG10mg - AQ10mg   | 74.052                   | 53.537                             | 94.567  | *** |
| DG100mg - DG10mg  | -3.109                   | -23.624                            | 17.406  |     |
| DG100mg - AQ100mg | 64.496                   | 43.981                             | 85.011  | *** |
| DG100mg - AQ10mg  | 70.942                   | 50.427                             | 91.457  | *** |
| AQ100mg - DG10mg  | -67.605                  | -88.120                            | -47.090 | *** |
| AQ100mg - DG100mg | -64.496                  | -85.011                            | -43.981 | *** |
| AQ100mg - AQ10mg  | 6.447                    | -14.068                            | 26.962  |     |
| AQ10mg - DG10mg   | -74.052                  | -94.567                            | -53.537 | *** |
| AQ10mg - DG100mg  | -70.942                  | -91.457                            | -50.427 | *** |
| AQ10mg - AQ100mg  | -6.447                   | -26.962                            | 14.068  |     |

***Tukey's Studentized Range (HSD) Test for Fasted vs Fed Digestion Percent Recoveries***

| Comparisons significant at the 0.05 level are indicated by ***. |                          |                                    |         |  |
|-----------------------------------------------------------------|--------------------------|------------------------------------|---------|--|
| Group Comparison                                                | Difference Between Means | Simultaneous 95% Confidence Limits |         |  |
| DG10mg Fasted- DG100mg Fed                                      | 3.109                    | -17.406                            | 23.624  |  |
| DG10mg Fasted- DG10mg Fed                                       | 67.605                   | 47.090                             | 88.120  |  |
| DG100mg Fasted- DG10mg Fed                                      | 74.052                   | 53.537                             | 94.567  |  |
| DG100mg Fasted - DG100mg Fed                                    | -3.109                   | -23.624                            | 17.406  |  |
| AQ10mg Fasted- AQ100mg Fed                                      | -67.605                  | -88.120                            | -47.090 |  |
| AQ10mg Fasted- AQ10mg Fed                                       | -64.496                  | -85.011                            | -43.981 |  |
| AQ100mg Fasted- AQ10mg Fed                                      | 6.447                    | -14.068                            | 26.962  |  |
| AQ100mg Fasted - AQ100mg Fed                                    | -74.052                  | -94.567                            | -53.537 |  |

**Table S5.** ANOVA analysis of variance using Tukey's Studentized Range (HSD) Test with SAS University Edition for comparison of micellarization efficiencies of digestion in both Fed and Starved digestion experiments. ME: Micellarization Efficiency.

***Tukey's Studentized Range (HSD) Test for Fasted Digestion Micellization Efficiency***

| Comparisons significant at the 0.05 level are indicated by ***. |                          |                                    |       |  |
|-----------------------------------------------------------------|--------------------------|------------------------------------|-------|--|
| ME Comparison                                                   | Difference Between Means | Simultaneous 95% Confidence Limits |       |  |
| CBD100mg - CBD10mg                                              | 0.309                    | -4.685                             | 5.303 |  |
| CBD10mg - CBD100mg                                              | -0.309                   | -5.303                             | 4.685 |  |

***Tukey's Studentized Range (HSD) Test fo Fed Digestion Micellization Efficiencies***

Comparisons significant at the 0.05 level are indicated by \*\*\*.

| ME Comparison      | Difference Between Means | Simultaneous 95% Confidence Limits |        |     |
|--------------------|--------------------------|------------------------------------|--------|-----|
| CBD100mg - CBD10mg | 8.408                    | 2.302                              | 14.514 | *** |
| CBD10mg - CBD100mg | -8.408                   | 14.514                             | -2.302 | *** |

***Tukey's Studentized Range (HSD) Test for Fasted vs Fed State Digestion Micellarization Efficiencies***

Comparisons significant at the 0.05 level are indicated by \*\*\*.

| ME Comparison                  | Difference Between Means | Simultaneous 95% Confidence Limits |         |     |
|--------------------------------|--------------------------|------------------------------------|---------|-----|
| CBD100mg Fasted - CBD10mg Fed  | 10.447                   | -11.078                            | 36.872  |     |
| CBD10mg Fasted- CBD100mg Fed   | 89.575                   | 60.914                             | 95.570  | *** |
| CBD100mg Fasted- CBD 100mg Fed | 91.405                   | 56.731                             | 101.976 | *** |
| CBD10mg Fed- CBD10mg Fasted    | -25.842                  | -90.587                            | -57.701 |     |

***Tukey's Studentized Range (HSD) Test for Fasted vs Fed Digestion Digestive Stability***

Comparisons significant at the 0.05 level are indicated by \*\*\*.

| Digestive Stability<br>Comparison | Difference<br>Between<br>Means | Simultaneous 95%<br>Confidence Limits |        |  |
|-----------------------------------|--------------------------------|---------------------------------------|--------|--|
| CBD100mg Fasted - CBD10mg Fed     | 3.127                          | -13.780                               | 19.487 |  |
| CBD10mg Fasted- CBD100mg Fed      | -3.109                         | -19.908                               | 13.764 |  |
| CBD100mg Fasted– CBD 100mg Fed    | 13.845                         | -6.768                                | 41.314 |  |
| CBD10mg Fed– CBD10mg Fasted       | -12.602                        | -24.557                               | 5.598  |  |