

| | Pepsin from porcine gastric mucosa | Rabbit gastric extract | Pancreatin from porcine pancreas | Lipase from porcine pancreas | Porcine bile extract |
|---|------------------------------------|------------------------|----------------------------------|------------------------------|----------------------|
| Pepsin activity (units/mg powder) | 2530.96 ± 134.28 | 468.88 ± 10.03 | / | / | / |
| Trypsin activity (TAME units/mg powder) | / | / | 10.40 ± 0.28 | 5.63 ± 0.29 | / |
| Lipase activity (units/mg powder) | / | 13.44 ± 0.65 | 49.27 ± 3.07 | 24.87 ± 2.10 | / |
| Bile salt concentration (mmol/g powder) | / | / | / | / | 1.62 ± 0.20 |

Table S1 Enzyme activity and bile salt concentration for *in vitro* simulated gastrointestinal digestion

TAME: p-toluene-sulfonyl-l-arginine methyl ester.

Table S2 Chemical composition of coffee pulp extracts obtained by different extraction methods

| Samples | sc-CO ₂ extract | Water extract | EtOH extract |
|------------------------------------|-----------------------------|---------------------------|----------------------------|
| Lipid content (mg/g) | 381.89 ± 30.21 ^c | 30.02 ± 2.44 ^a | 136.72 ± 8.17 ^b |
| Protein content (mg/g) | 9.62 ± 0.92 ^b | 8.23 ± 0.42 ^a | 7.72 ± 0.11 ^a |
| Total flavonoid content (mg CE/g) | 24.76 ± 0.75 ^b | 17.02 ± 0.96 ^a | 16.64 ± 1.12 ^a |
| Caffeine (mg/g)* | 106.32 ± 5.54 ^c | 20.48 ± 0.58 ^a | 36.79 ± 1.66 ^b |
| Total phenolic content (mg GAE/g)* | 43.56 ± 1.20 ^b | 75.96 ± 2.93 ^c | 35.10 ± 2.55 ^a |
| Protocatechuic acid (mg/g)* | 14.85 ± 1.22 ^c | 5.21 ± 0.05 ^a | 7.75 ± 0.35 ^b |
| Chlorogenic acid (mg/g)* | 0.63 ± 0.10 ^a | 5.79 ± 0.12 ^c | 4.72 ± 0.07 ^b |

Different letters (a-c) indicate significant differences according to Tukey's test ($p < 0.05$) for the same components across different extracts. Data marked with asterisks (*) are from a previously published study (Reference 6). CE: catechin equivalents; GAE: gallic acid equivalent.

Table S3 Enrichment analysis showing significantly modulated biological processes and signaling pathways using differential cytokines of each digesta group compared to positive control group

| Samples | sc-CO ₂ | EtOH | Water | StdMix |
|---|--------------------|--------------------------|--------------|---------------|
| Differential cytokine proteins | IL-1 β | IL-1ra | IL-1 β | IL-1 β |
| | IL-10 | IL-10 | IL-10 | IL-1ra |
| | TNF- α | TNF- α | IL-10 | IL-10 |
| | IL-6 | IL-6 | IL-6 | TNF- α |
| | CCL2 | CCL2 | CCL2 | IL-6 |
| | | | | CCL2 |
| Biological process | | -Log ₁₀ (FDR) | | |
| Cellular response to lipopolysaccharide | 5.79 | 4.06 | 4.10 | 5.77 |
| Regulation of cell-cell adhesion | 5.53 | 4.14 | 3.82 | 5.65 |
| Regulation of chemokine production | 5.38 | 3.30 | 3.42 | 5.62 |
| Regulation of epithelial cell apoptotic process | 5.29 | 4.14 | 3.39 | 5.07 |
| Regulation of inflammatory response | 4.97 | 4.10 | 3.42 | 4.95 |
| Regulation of interleukin-6 production | 4.94 | 2.92 | 3.07 | 4.54 |
| Regulation of receptor signaling pathway via JAK-STAT | 4.33 | 3.82 | 2.25 | 4.36 |
| Cytokine-mediated signaling pathway | 3.92 | 2.15 | 2.31 | 4.09 |
| Regulation of MAPK cascade | 3.55 | 1.91 | 2.10 | 3.51 |
| Regulation of interleukin-1 production | 3.52 | 3.15 | 1.70 | 3.24 |
| Regulation of signaling receptor activity | 3.11 | 2.16 | 2.23 | 3.15 |
| Regulation of cell junction assembly | 2.72 | nd | nd | 2.55 |
| Regulation of macrophage activation | 2.31 | 2.05 | 2.11 | 2.15 |
| Regulation of canonical NF-kappaB signal transduction | 2.21 | nd | nd | 2.04 |
| Regulation of organic acid transport | 2.15 | nd | nd | 1.99 |
| Signaling pathway | | -Log ₁₀ (FDR) | | |
| Cytokine-cytokine receptor interaction | 7.45 | 4.85 | 5.53 | 8.81 |
| Inflammatory bowel disease | 7.45 | 6.97 | 5.18 | 7.10 |
| TNF signaling pathway | 6.88 | 4.35 | 4.74 | 6.41 |
| NOD-like receptor signaling pathway | 6.21 | 3.85 | 4.26 | 5.74 |
| Toll-like receptor signaling pathway | 4.71 | 2.54 | 2.72 | 4.42 |
| NF-kappa B signaling pathway | 2.66 | nd | nd | 2.48 |
| JAK-STAT signaling pathway | 2.35 | 2.23 | 2.40 | 2.17 |
| MAPK signaling pathway | 1.88 | nd | nd | 1.71 |

FDR: false discovery rate; nd: significant enrichment was not detected. IL-1 β : interleukin-1 beta; IL-1ra: interleukin-1 receptor antagonist; IL-10: interleukin-10; TNF- α : tumor necrosis factor alpha; IL-6: interleukin-6; CCL2: C-C motif chemokine ligand 2; JAK-STAT: janus kinase-signal transducer and activator of transcription; MAPK: mitogen-activated protein kinase; NF-kappaB: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF: tumor necrosis factor signaling pathway; NOD-like: nucleotide-binding oligomerization domain-like.

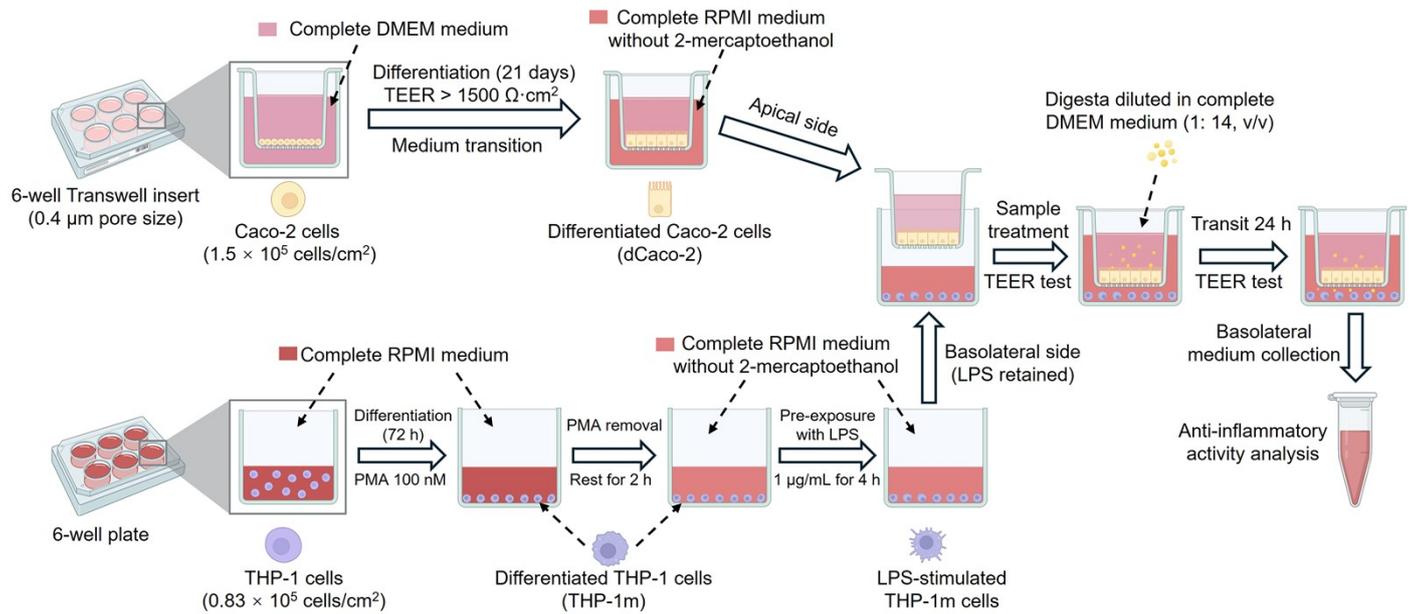


Fig. S1 Schematic representation of the assembly protocol of Caco-2/THP-1 co-culture model. dCaco-2: differentiated Caco-2 cells (monolayer); LPS: Lipopolysaccharide; THP-1m: differentiated THP-1 cells (macrophages); PMA: phorbol myristate acetate. TEER: transepithelial electrical resistance; DMEM: dulbecco's modified eagle medium; RPMI: roswell park memorial institute 1640 medium.

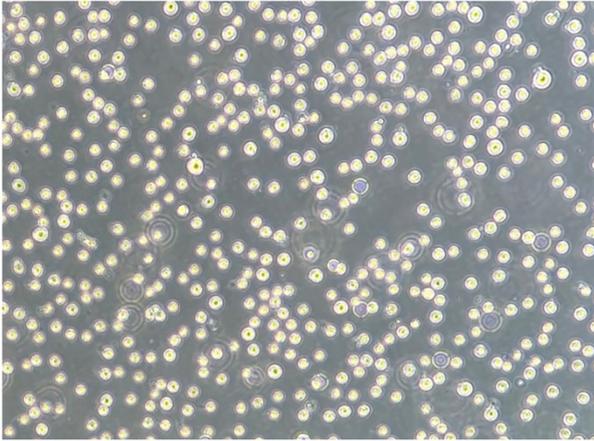
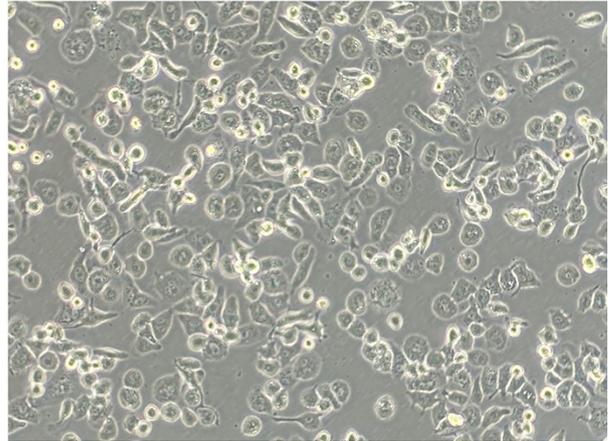
A**B**

Fig. S2 Morphological changes (100×) in THP-1 cell differentiation induced by **phorbol 12-myristate 13-acetate (PMA, 100 nM)** at A) 0 h and B) 72 h. Cell morphology changed from a rounded shape to elongated and flattened shape.