

Bacterial enterolignans depleted in Alzheimer's disease prevent neuroinflammation by attenuating leukocyte-endothelial interactions

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Background

Alzheimer's disease (AD) is the most common type of dementia which is caused by neuroinflammation exacerbated by peripheral inflammation such as illness and infection. Evidence has emerged which suggests immune cells from the peripheral blood, such as neutrophils and T helper cells, contribute to neuroinflammation and neurocognitive decline. It is not currently known what drives immune cells infiltration into the brain parenchyma past the blood-brain barrier (BBB), why immune cells are permitted to bypass this highly selective protection of the brain, or why some older adults might be resilient to the sequelae of neuroinflammation.

Enterolactone is decreased in Alzheimer's disease

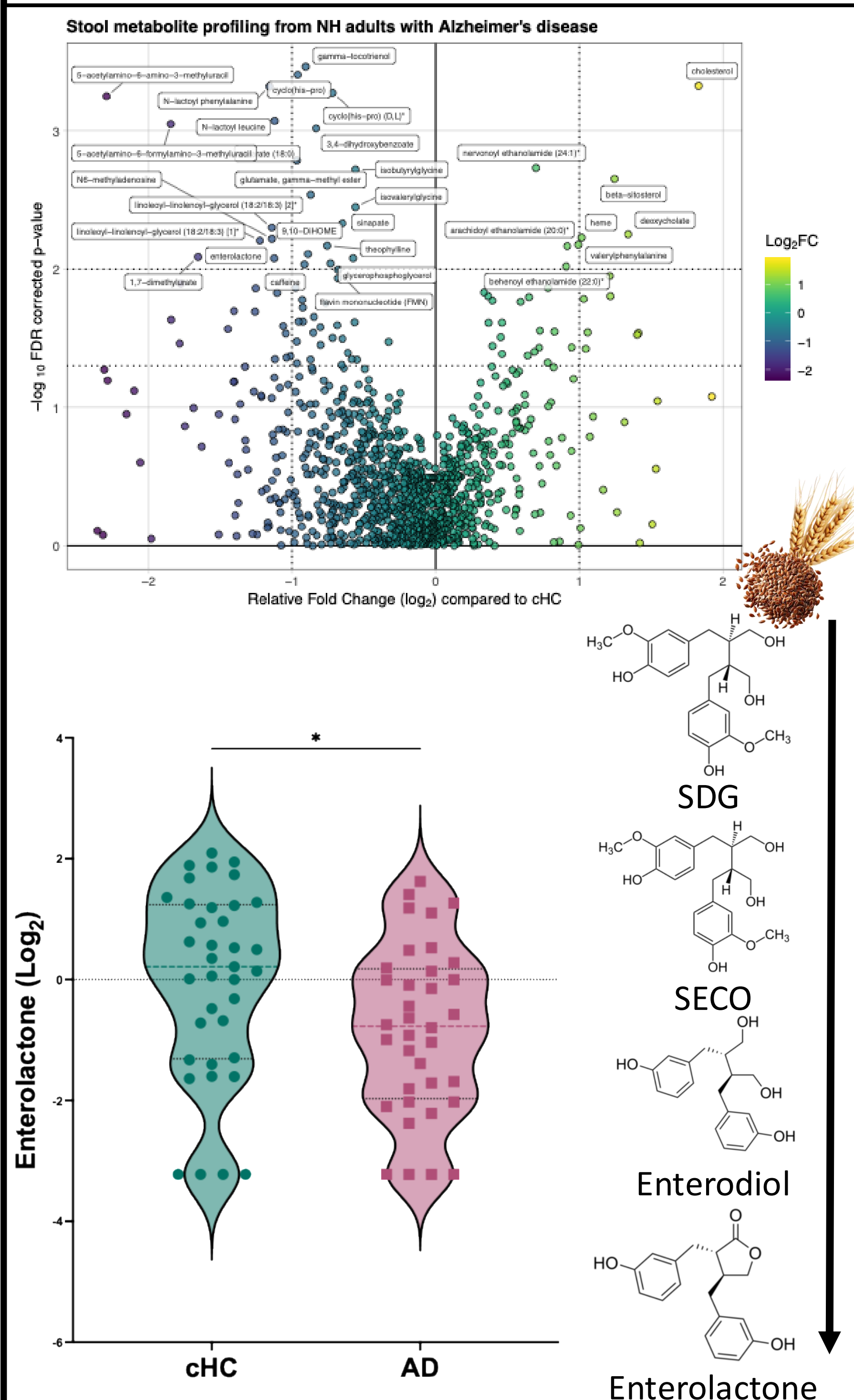


Fig 1. Top. Enterolactone is depleted in AD. **Bottom.** Enterolactone is produced by microbial metabolism of dietary macronutrients.

Intestinal microbiota are associated with the metabolism of dietary lignans to enterolactone

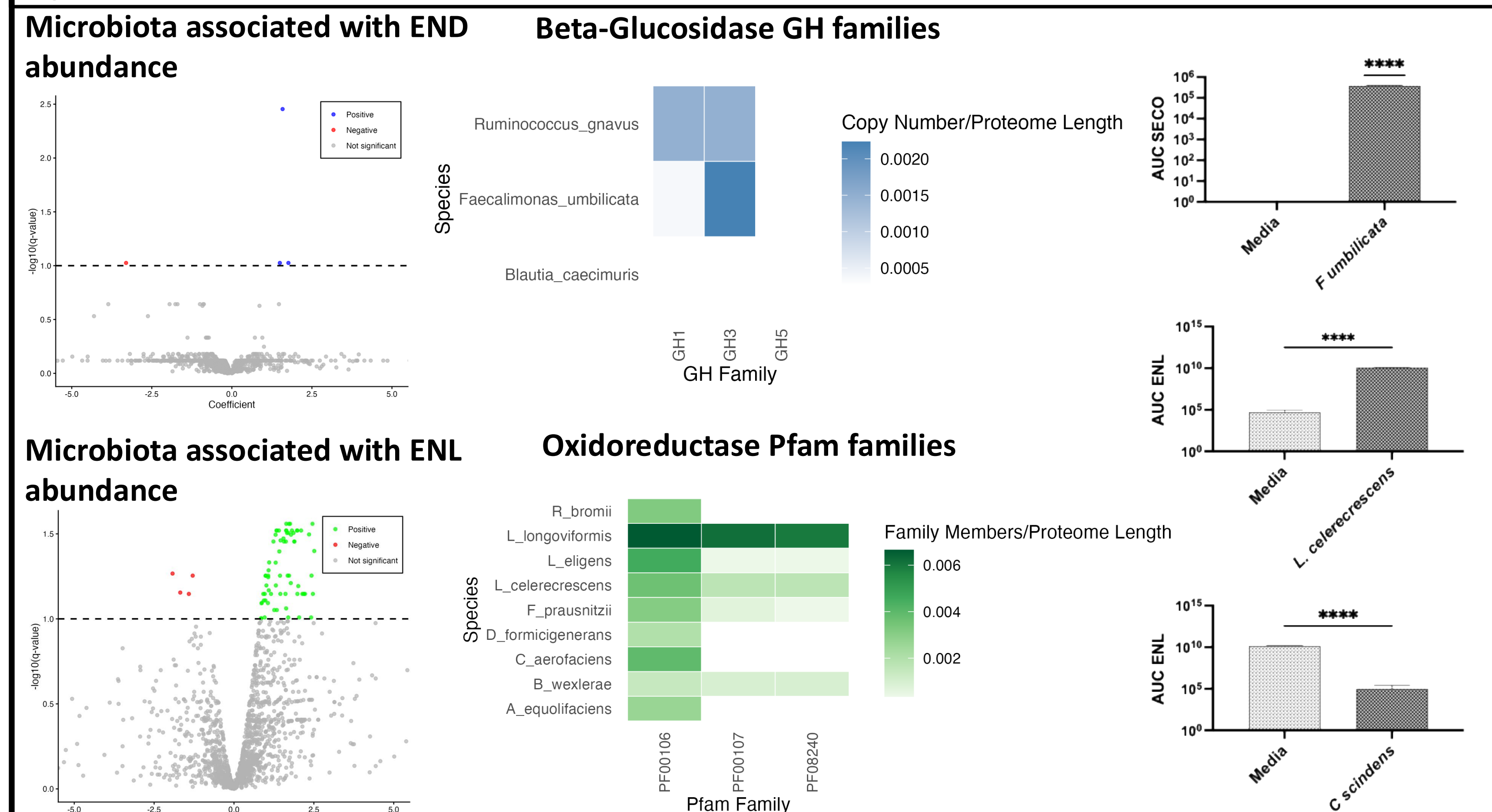


Fig 2. Top. Candidate bacteria responsible for the metabolism of SDG were identified using linear modeling and β -glucosidase family abundance analysis. **Below.** Candidate bacteria responsible for the metabolism of END were identified using linear modeling and oxidoreductase family abundance analysis. **Right.** Bacterial production of SECO, enterolactone, and degradation of enterolactone.

Enterolactone blocks O-linked glycosylation of T-lymphocytes and endothelial cells

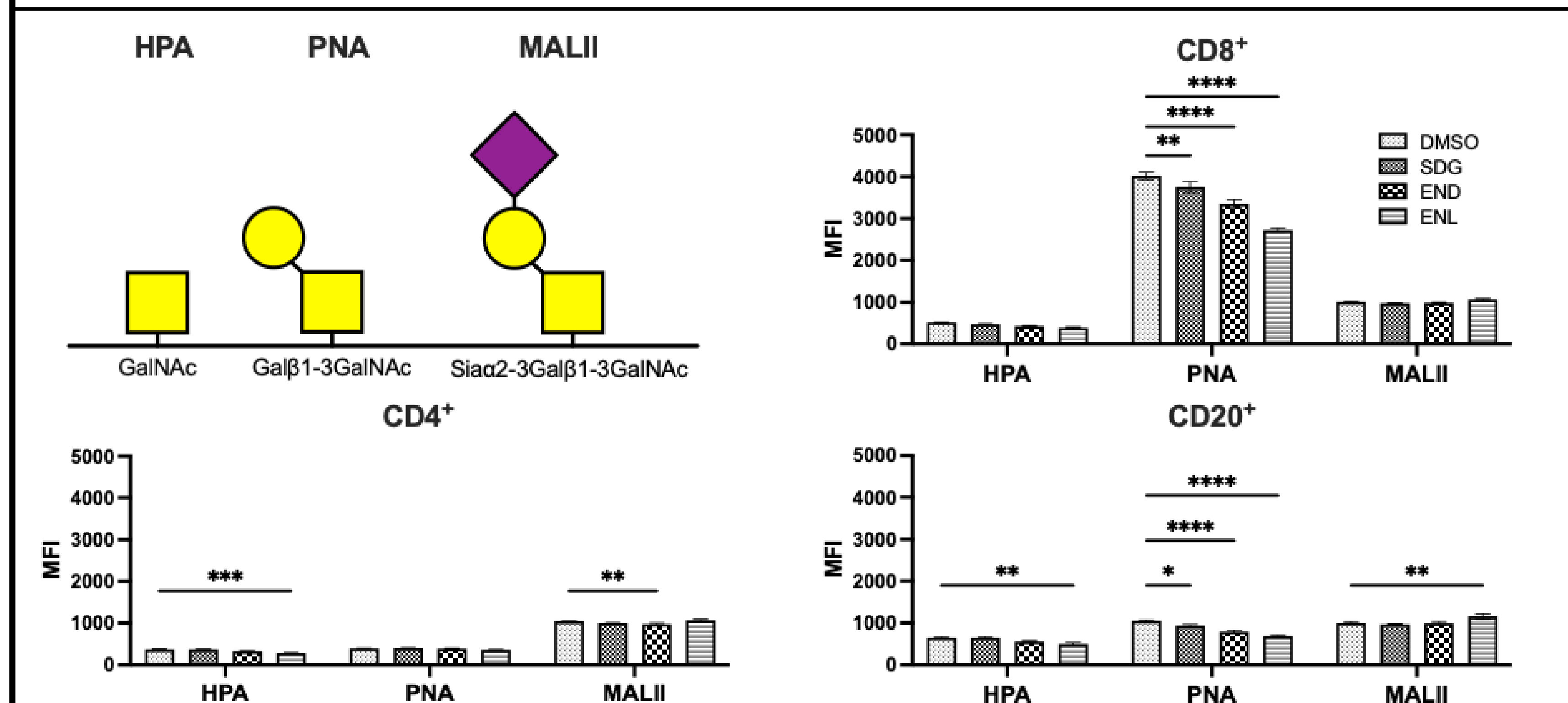


Fig 3. Top Left. Helix pomatia agglutinin (HPA), Peanut Agglutinin (PNA), and Maackia amurensis lectin II (MALII) recognize the Tn-antigen GalNAc, T-antigen Gal- β (1-3)-GalNAc, and α -2,3 sialic acid, respectively. Lectin binding to CD8⁺ T cells (**Top Right**), CD4⁺ T cells (**Bottom Left**), or CD20⁺ B cells (**Bottom Right**) treated with DMSO (vehicle), SDG, enterodiol (END) or enterolactone (ENL). One-way ANOVA * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$.

Enterolactone inhibits GalNAc-Transferase enzymes

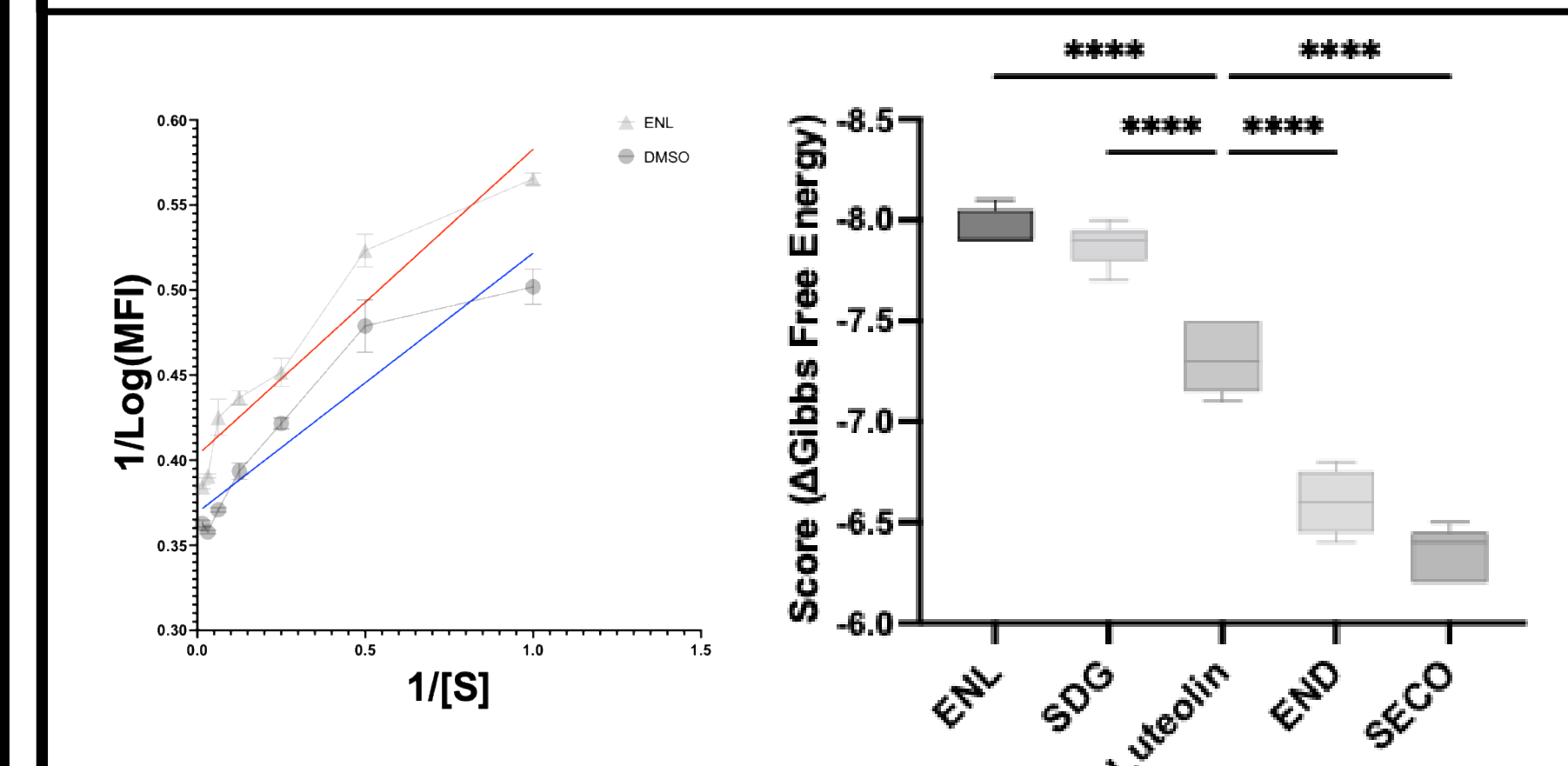


Fig 4. Left. Lineweaver-Burke plot of HL-60 cells cultured with UDP-GalNAc and enterolactone (ENL) or DMSO (vehicle). **Right.** Molecular docking of enterolactone (ENL), SDG, luteolin, enterodiol (END), or SECO into polypeptide binding pocket of GalNAc-transferase 2. Unpaired t-test * $p \leq 0.05$, ** $p \leq 0.01$ *** $p \leq 0.001$.

Enterolactone degrading bacteria are associated with dementia severity

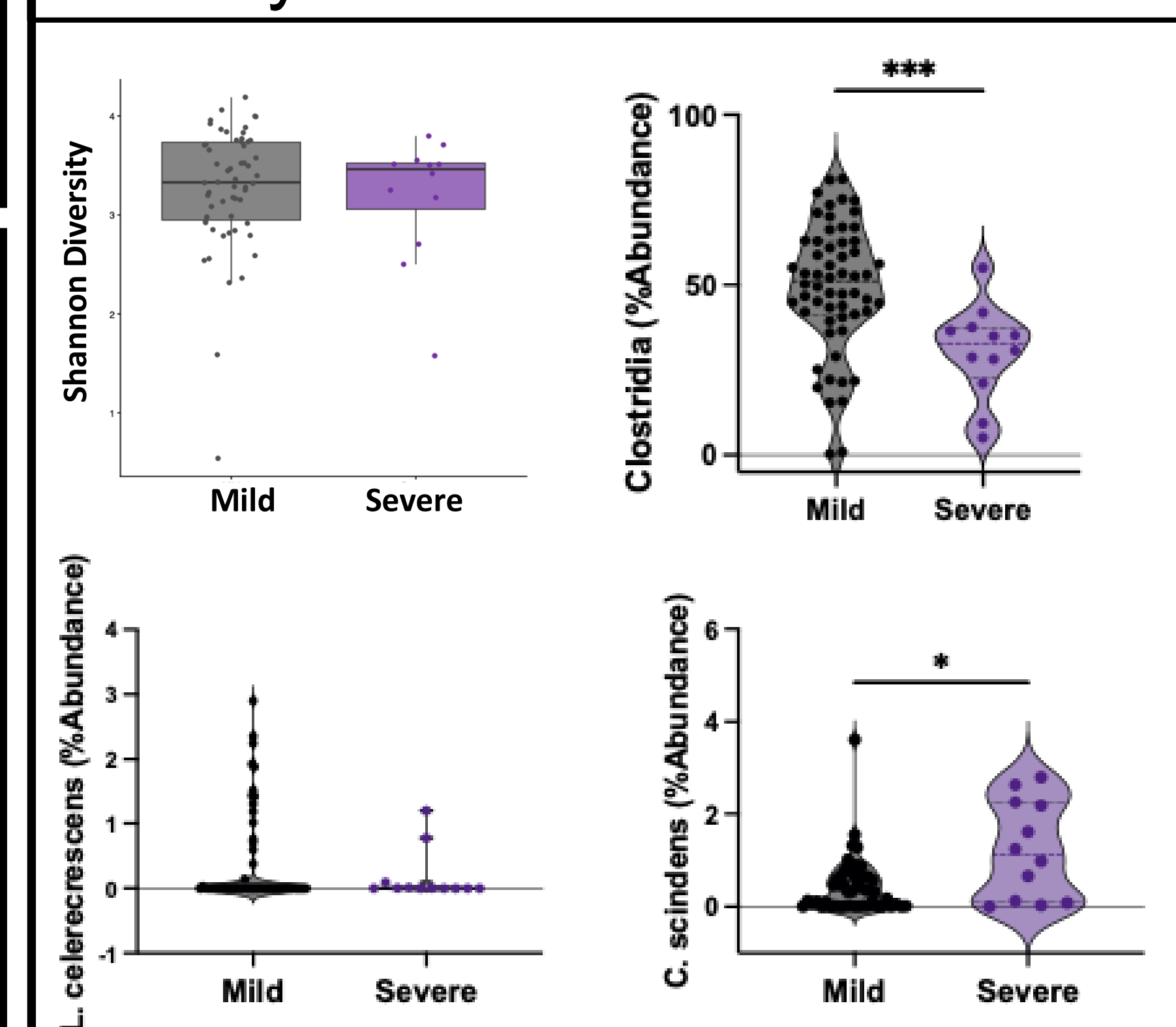


Fig 5. Top Left. Shannon diversity of mild (CDR ≤ 2) and severe (CDR=3) dementia. **Top right.** Abundance of order Clostridia. **Bottom Left.** Abundance of *L. celerecrescens*. **Bottom right.** Abundance of *C. scindens*. Unpaired t-test * $p \leq 0.05$, ** $p \leq 0.01$ *** $p \leq 0.001$.

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