**Larazotide, an Intestinal Permeability Modulator, Exacerbates Renal Injury and Alters the Gut Microbiome in a Diabetic Kidney Disease Model**

**Aims:**
The gut-kidney axis has emerged as a potential contributor to diabetic kidney disease (DKD), with intestinal barrier dysfunction implicated in disease progression. This study evaluated whether larazotide, a peptide that modulates intestinal permeability, could ameliorate DKD features in db/db mice.

**Methods:**
Eight-week-old db/db mice (n=15) were treated with larazotide (20 mg/kg/day) in drinking water for 10 weeks. Intestinal permeability was assessed *in vivo* using FITC-dextran. Markers of kidney damage included urinary albumin-creatinine ratio (UACR) and glomerulosclerosis scoring by periodic acid-Schiff (PAS) staining. Water intake, urine volume, and gut transit time were measured. Caecal microbial composition was profiled using 16S rRNA sequencing. Data were analysed using two-way ANOVA.

**Results:**
Diabetic db/db mice exhibited significantly increased intestinal permeability compared to non-diabetic controls (*p* < 0.0001). Larazotide treatment did not improve intestinal permeability and was associated with greater albuminuria (*p* = 0.0087) and kidney-to-body weight ratio (*p* = 0.0046) in db/db mice. Larazotide-treated diabetic mice also displayed increased water intake (*p* = 0.0017), urine output (*p* = 0.0011), and delayed gut transit (*p* = 0.0178). 16S rRNA sequencing revealed that larazotide altered microbial beta diversity in db/db mice (*p* = 0.0072) and reduced the Firmicutes/Bacteroidetes ratio in larazotide-treated non-diabetic controls (*p* = 0.0232).

**Conclusion:**
In this study, larazotide did not improve intestinal barrier dysfunction or renal outcomes in db/db mice and was associated with changes in renal markers and gut microbiota composition. These findings indicate that the effects of larazotide in the context of diabetes warrant further investigation to better understand its safety profile and potential impact on kidney and gut health in DKD.