

**Figure 1**. Quality evaluation of XSP. (A) Image showing the overall appearance traits of XSP. (B) SEM images showing the cross-section of XSP. (C) The HPLC properties of the representative component cucurbitacin IIa in XSP. (D) Graph showing the in vitro release of XSP at 0-12 h.



**Figure 2**. XSP treatment remarkably alleviates DSS-induced colitis in rats.

1. Flow chart of animal treatment (n = 10). (B) The changes of body weight

(n = 6-10). (C) Disease Activity Index (DAI) scores (n = 6-10). (D) The colon lengths in different groups (n=6-10). Data were represented as mean ± SEM. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001.



**Figure 3**. H&E staining of colon tissues and the activities of NO and MPO.

1. The epithelial damage, inﬂammatory cell inﬁltration, and crypt lesions in

different groups were evaluated by H&E staining and pathological scores were quantiﬁed in a bar graph. (B) The activities of MPO and NO were determined to indicate the degree of inﬂammation in colon tissue. Data are represented as mean ± SEM. \**p* < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001.



**Figure 4.** The protein levels of proinflammatory cytokines (A) TNF-α, (B) IL-β1, (C) IL-6, and (D) IL-10 in serum of control, DSS, LXSP, MXSP, and HXSP groups. Data are represented as mean ± SEM. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001.



**Figure 5.** XSP reprograms gut microbiota and increases the abundance of SCFA-producing bacteria. (A) Principal component analysis (PCA) and principal

coordinate analysis (PCoA) of gut microbial communities in control, DSS, and MXSP groups. (B) Fecal microbiota composition at the family level. (C) Fecal microbiota composition at the genus level and the proportions of Lactobacillus, Bacteroidetes, Escherichia-Shigella, and the Lachnospiraceae NK4A136 group. Data are represented as mean ± SEM. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001.



**Figure 6.** The relative levels of acetate, propionate, butyrate, pentanoate, and caproate in fecal samples. Data are represented as mean ± SEM. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001.



**Figure 7.** Differentially Expressed Genes (DEG) in colonic tissue. (A) The heatmap plot of DEGs in control, DSS, and MXSP groups. (B) Venn diagram of DEGs with DSS vs. control and DSS vs. MXSP. (C) The volcano plot of DEGs between DSS vs. control and DSS vs. MXSP in colonic tissue. Note: The black dots represent genes without different expression between two groups. The red dots show genes that were upregulated and the green dots those that were downregulated.



**Figure 8.** KEGG pathway analysis of DEGs. (A)Signiﬁcant pathways involving DEGs between DSS and control groups. (B)Signiﬁcant pathways involving DEGs between DSS and MXSP groups. (C) Heatmap plot of genes in the MAPK signaling pathway.