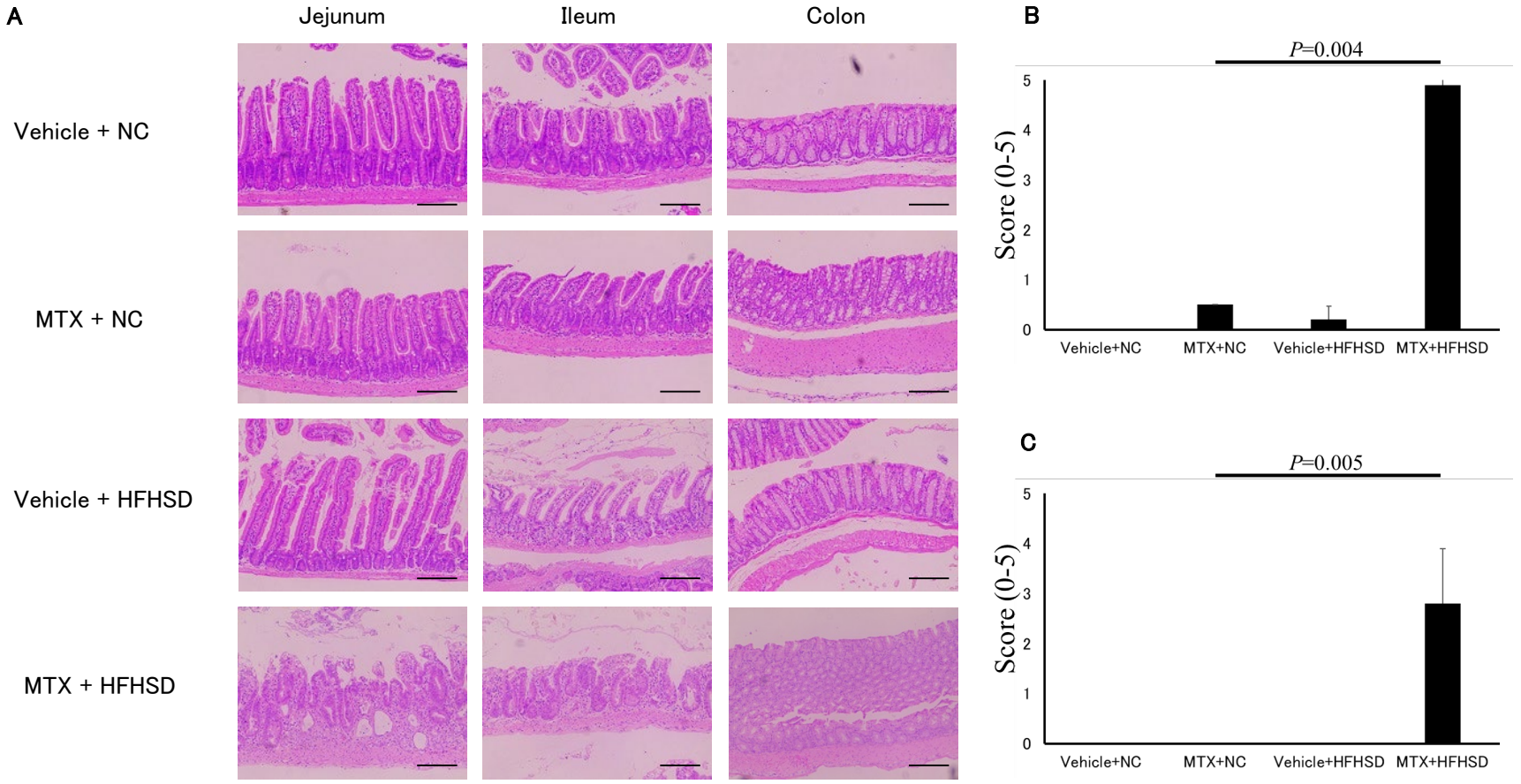
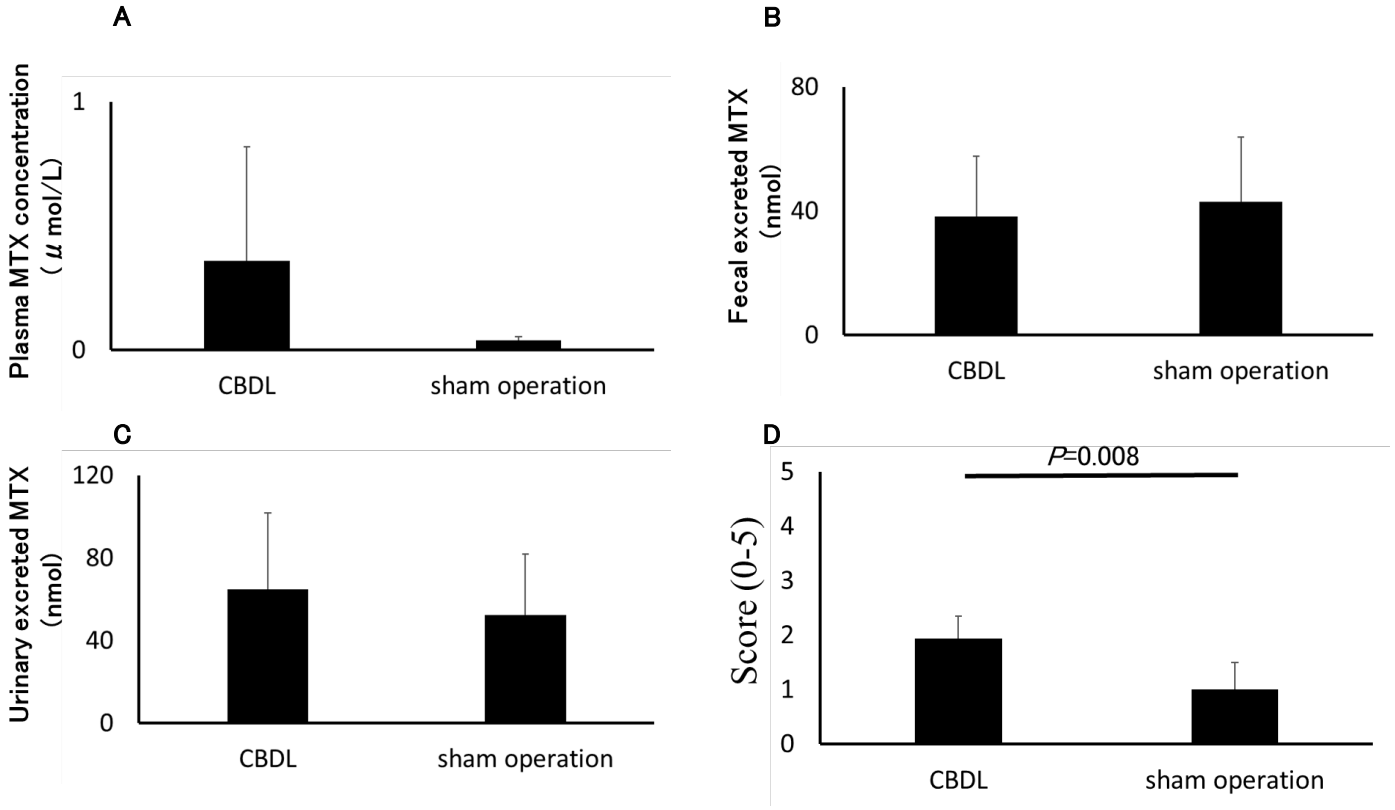
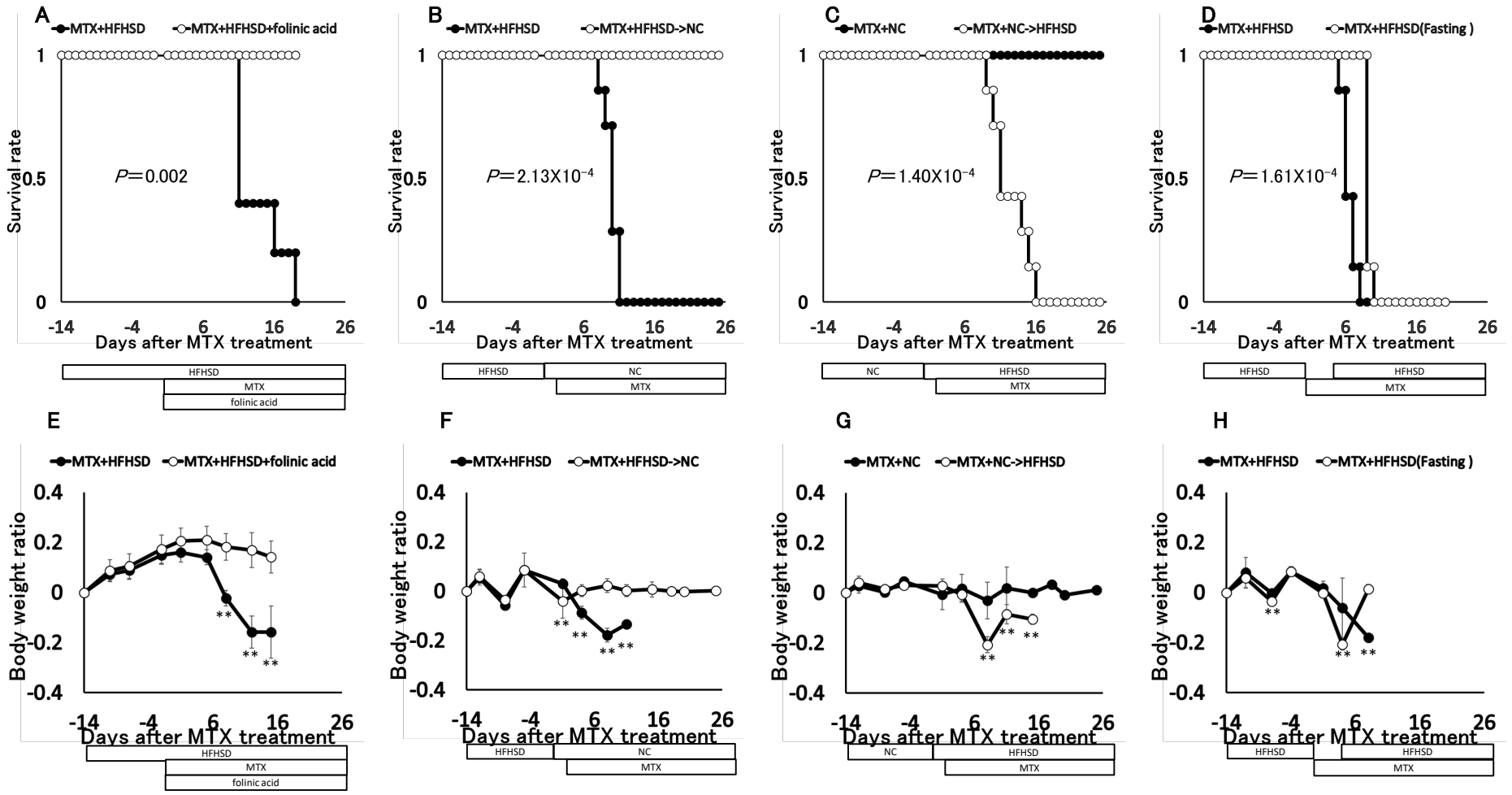


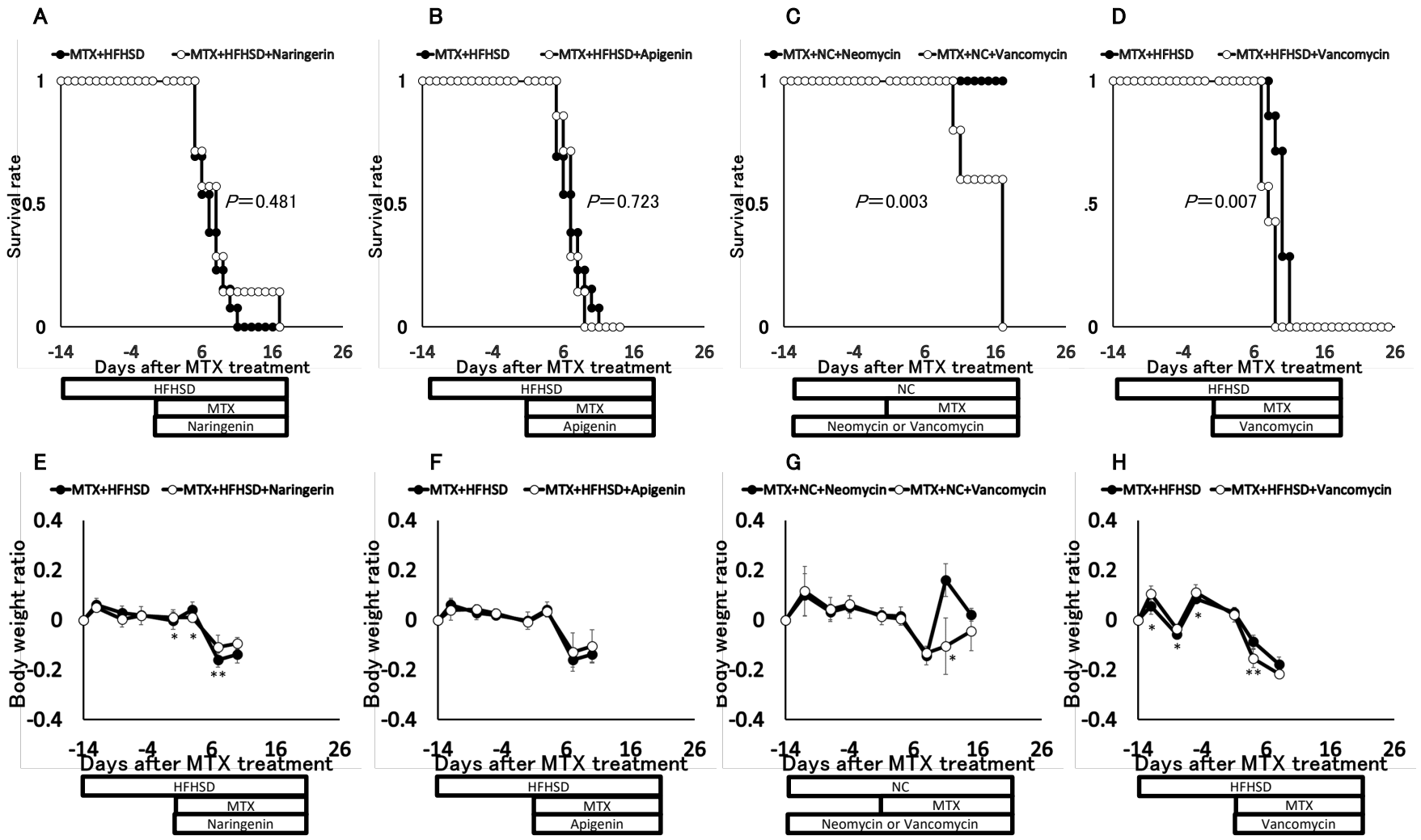
Supplementary Figure S1. Histological analyses of mouse intestine. (A) Representative histological images with hematoxylin and eosin stain of jejunum, ileum, and colon in each mouse group. Histological score of jejunum (B) and ileum (C) in each mouse group (Mean ± SD, n=5) was evaluated, as previously described [20-22]. Difference was tested by Mann-Whitney's U test. MTX: methotrexate, NC: normal chow, HFHSD: high fat high sucrose diet. Scale bars: 200μm



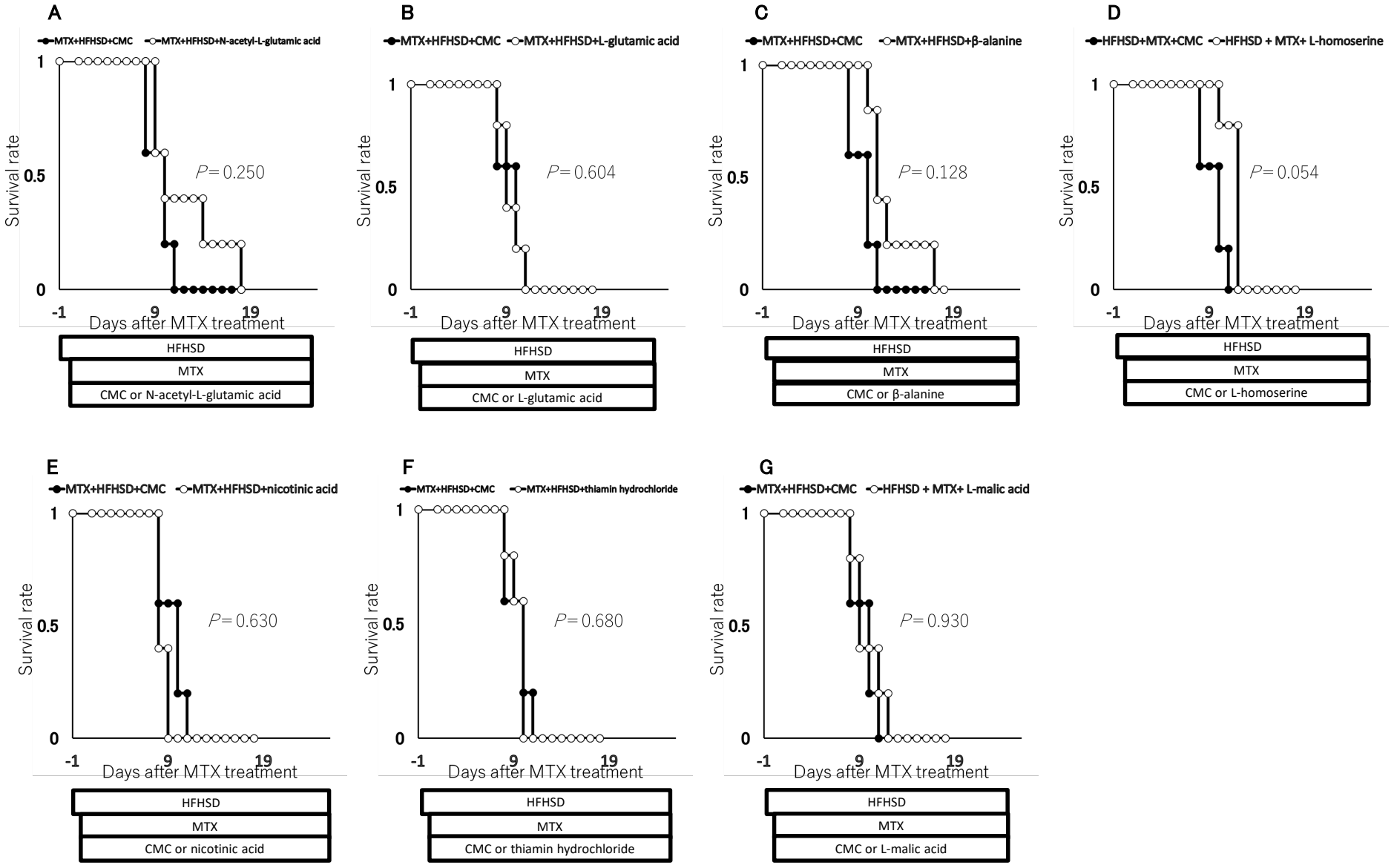
Supplementary Figure S2. MTX disposition after common bile duct ligation. (A) MTX concentration in plasma on day 4, 24 hours after administration of MTX (Mean ± SD, MTX+HFHSD+sham operation; n=6, MTX+HFHSD+CBDL; n=6). MTX excretion in (B) feces and (C) urine for 24 hours on day 3 (Mean ± SD, MTX+HFHSD+sham operation; n=6 , MTX+HFHSD+CBDL; n= 6). (D) Histological scores of jejunum in each mouse group (Mean ± SD, MTX+HFHSD+sham operation; n=4, MTX+HFHSD+CBDL; n=5). Difference was tested by Mann-Whitney's U test. MTX: methotrexate, HFHSD: high fat high sucrose diet, CBDL: common bile duct ligation.



Supplementary Figure S3. The effect of folinic acid and the change of diet. (A-D) Survival rate in each mouse group. Difference was tested by log-rank test. (E-H) Body weight ratio in each mouse group. Difference was tested by one-way ANOVA and asterisks (**) indicate **p<0.01 (Mean ± SD, MTX+HFHSD [A, E]: n=5, MTX+HFHSD+folinic acid: n=5, MTX+HFHSD [B, C, D, F, G, H]: n=7, MTX+HFHSD→NC: n=7, MTX+NC→HFHSD: n=7, MTX+HFHSD(Fasting): n=7).). The results are representative of two independent experiments. MTX: methotrexate, NC: normal chow, HFHSD: high fat high sucrose diet, ANOVA: analysis of variance.



Supplementary Figure S4. The effects of flavonoids and antibiotics. (A-D) Survival rate in each mouse group. Difference was tested by log-rank test. (E-H) Body weight ratio in each mouse group. Difference was tested by one-way ANOVA and asterisks (* and **) indicate *p<0.05 and **p<0.01, respectively (Mean ± SD, MTX+HFHSD: n=13[A,B, E, F], MTX+HFHSD+naringenin: n=7, MTX+HFHSD+apigenin: n=7, MTX+NC+vancomycin: n=5, MTX+NC+neomycin: n=5, MTX+HFHSD: n=7 [D, H], MTX+HFHSD+vancomycin: n=7). The results are representative of two independent experiments. MTX: methotrexate, HFHSD: high fat high sucrose diet, ANOVA: analysis of variance.



Supplementary Figure S5. Effects of the metabolites on MTX enteritis. (A-G) Survival rate in each mouse group treated with the candidate metaboilites, N-acetyl-L-aspartic acid, nicotinic acid, L-glutamic acid, thiamin hydrochloride, β-alanine, L-malic acid, or L-homoserine (n=5). Difference was tested by log-rank test. MTX: methotrexate, CMC: carboxymethyl cellulose, HFHSD: high fat high sucrose diet.