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Mannan oligosaccharide attenuates cognitive and behavioral disorders in the 5xFAD Alzheimer's disease mouse model via regulating the gut microbiota-brain axis

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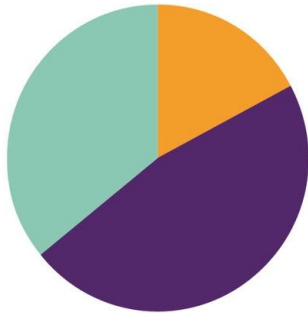
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Introduction

- Alzheimer's disease (AD) is a neurodegenerative disease
 - cerebral cortex and hippocampus → declining cognitive function
 - aggregation of A β in prefrontal cortex (PFC) and amygdala → emotion regulating regions → anxiety-like behavior



Total:
5.8 Million

65-74 years:
1 million (17%)

75-84 years:
2.7 million (47%)

85+ years:
2.1 million (36%)

- evidence suggests that the microbiota-gut-brain axis plays a pivotal role in adjusting brain functions
- altered gut microbiota appears to be associated with A β accumulation
- Lactobacillus and Bifidobacterium can improve the HPA axis function and modulate the behavior stress response
- prebiotic mannan oligosaccharide (MOS) treatment can reduce inflammation, prevent obesity, and strengthen the immune system via its mediating effects on gut microbiota
- beneficial microbial metabolites = short-chain fatty acids (SCFAs)

Alzheimer's Symptoms

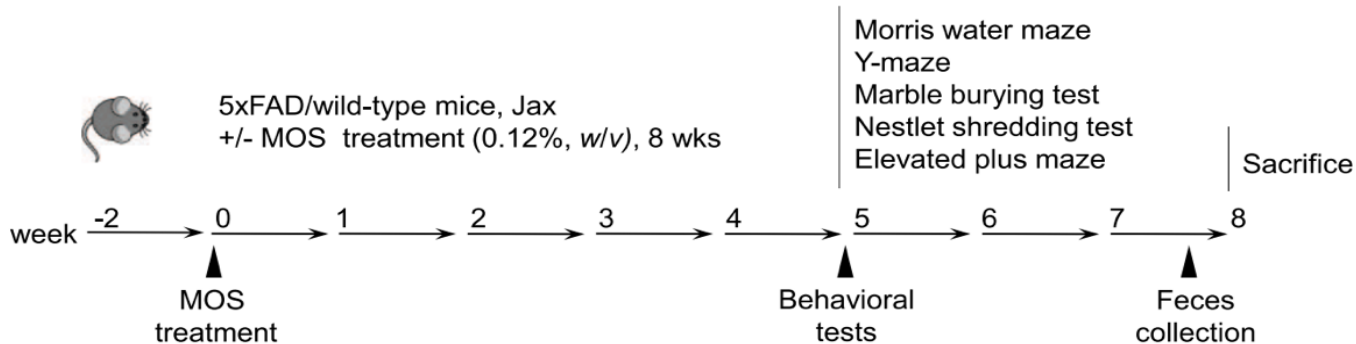


Materials and Methods

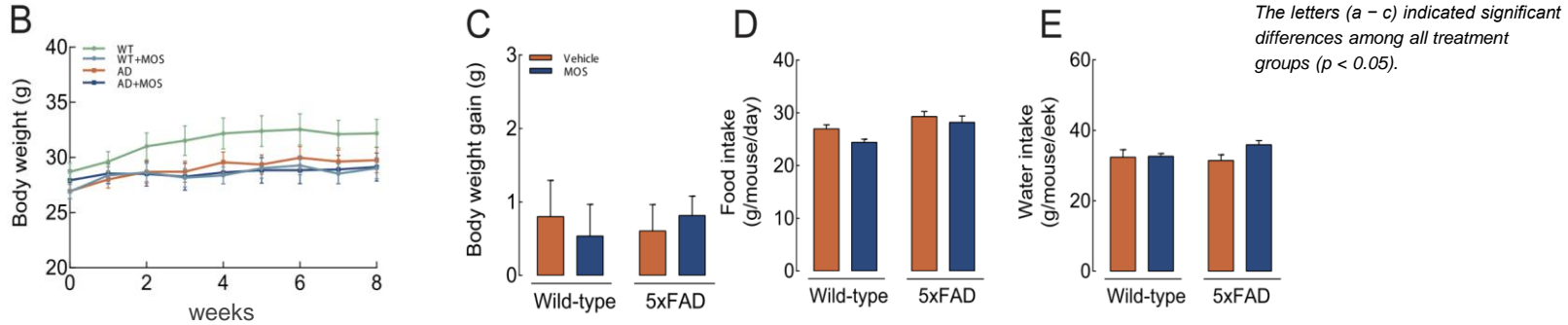
➤ Animals

- 6-month old **male 5xFAD-transgenic mice** and age-matched **wild-type mice (control)** were used
- The 5xFAD and wild-type (WT) mice were randomly divided into **6 groups** (6 months old, n = 8 per group):
 - WT group
 - WT + MOS group
 - WT + SCFAs group
 - 5xFAD group
 - 5xFAD + MOS group
 - 5xFAD + SCFAs group

The experimental workflow (48 mice total; 8 mice/group)



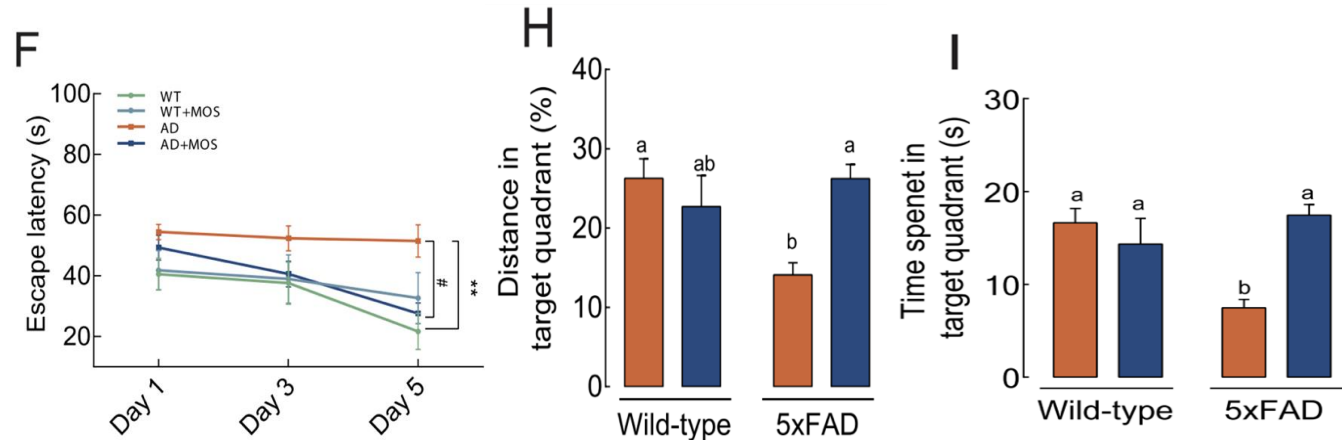
Effects of MOS Treatment on Cognitive Impairments and Behavioral Disorders in 5xFAD Mice.



MOS treatment had no effects on the energy intake and body weight changes in the AD mice

Morris water-maze test (MWM)

MOS improved cognitive deficits of AD mice.

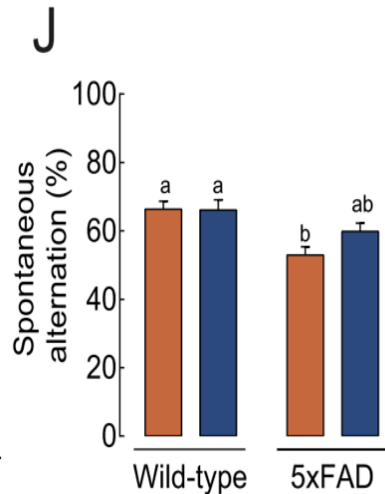


Effects of MOS Treatment on Cognitive Impairments and Behavioral Disorders in 5xFAD Mice. (ctd.)

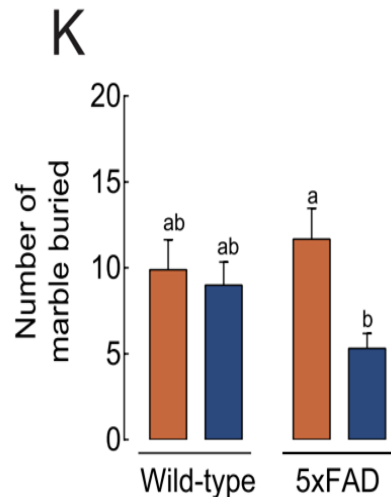
The letters (a - c) indicated significant differences among all treatment groups ($p < 0.05$).

MOS treatment had no significant improvement effects on working memory in AD mice

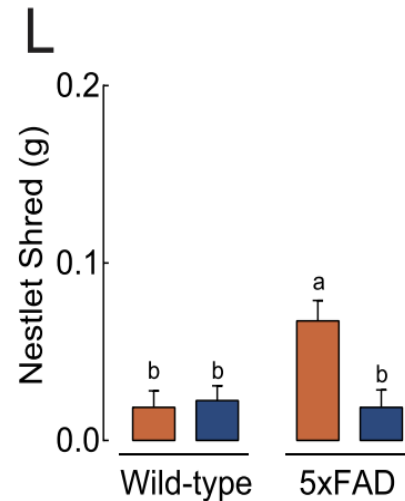
MOS attenuated anxiety-like behaviors in AD mice.



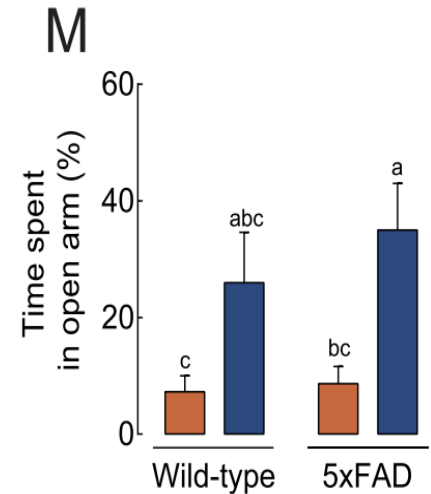
Y-maze test



marble-burying test (MBT)



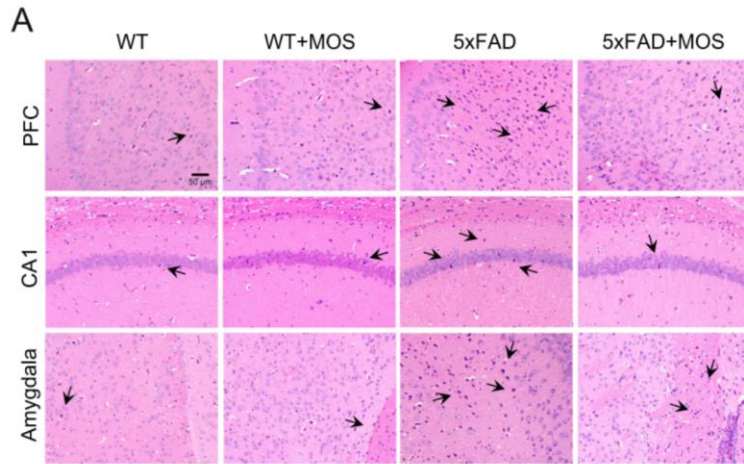
the nestlet shredding test (NST)



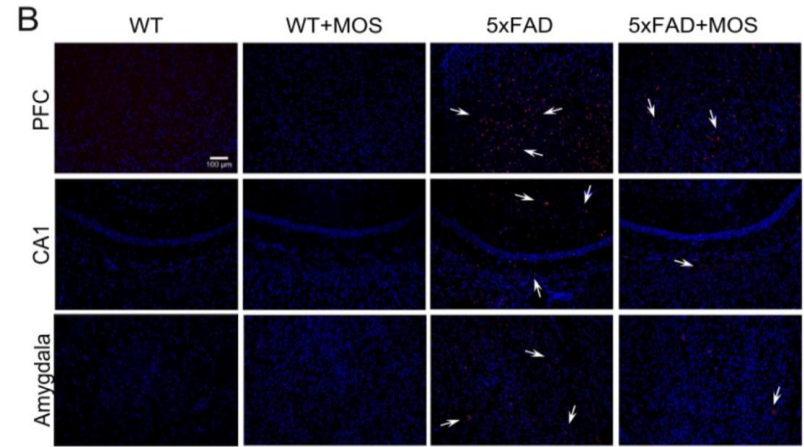
elevated plus-maze test (EPM)

Effects of MOS Treatment on Histopathological Changes and Amyloid Deposition of Brain in 5xFAD Mice.

H&E Stain



Immunofluorescence Stain



MOS reduced amounts of shrinking neurons and played a role in decreasing amyloid plaques.

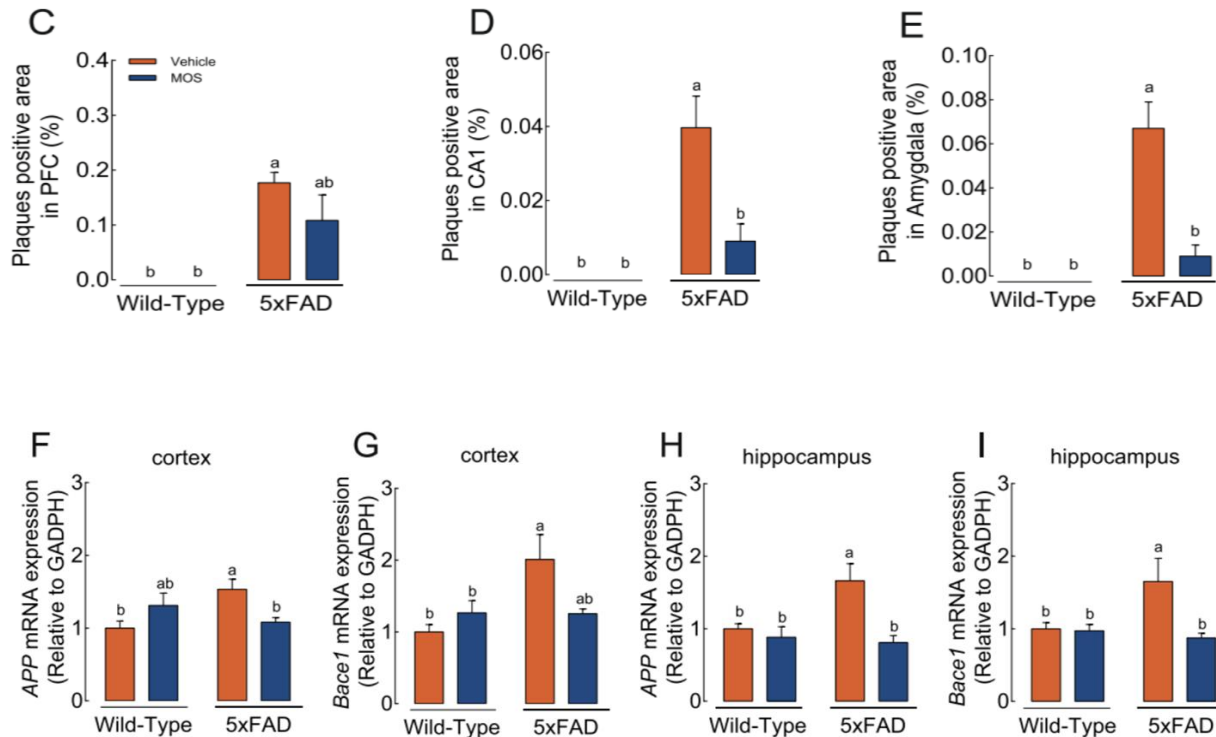
Effects of MOS Treatment on Histopathological Changes and Amyloid Deposition of Brain in 5xFAD Mice ctd.

Letters a - c, $p < 0.05$

Quantification of Amyloid Deposition Area

MOS improved neuronal morphology and the accumulation of amyloid.

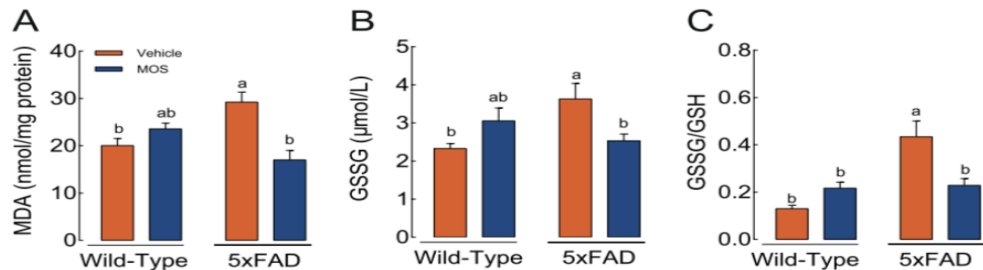
mRNA Expression of APP and BACE1



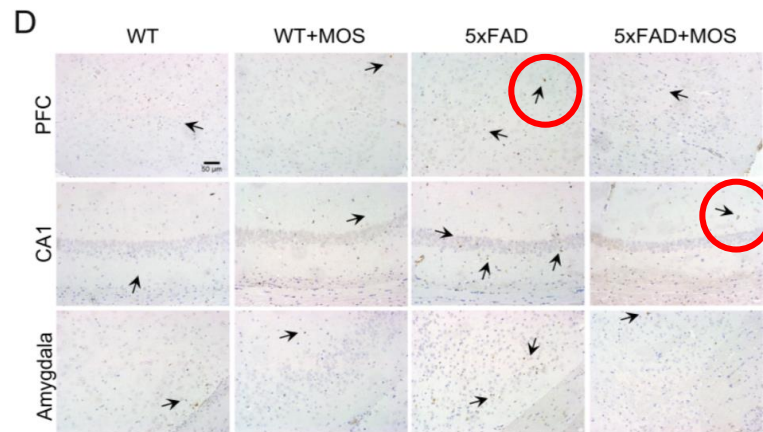
Effects of MOS Treatment on Oxidative Stress and Inflammatory Responses of Brain in 5xFAD Mice

Letters a - c, $p < 0.05$

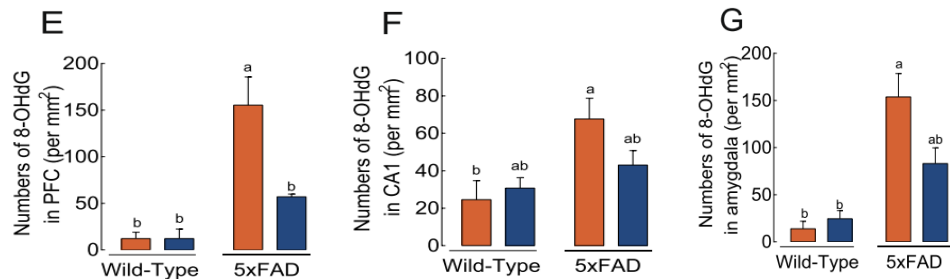
Levels of MDA, GSSG, & Ratio of GSSG/GSH



Immunohistochemistry (IHC) of 8-OHdG



Quantification of 8-OHdG Levels

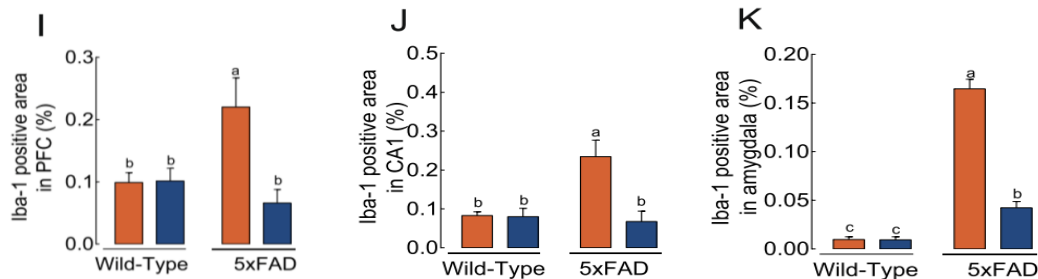


MOS reduced MDA, GSSG and 8-OHdG to decline factors of oxidative stress in AD mice.

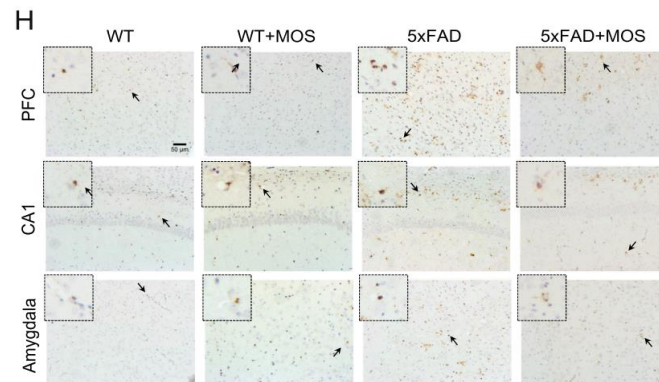
Effects of MOS Treatment on Oxidative Stress and Inflammatory Responses of Brain in 5xFAD Mice ctd.

Letters a - c, $p < 0.05$

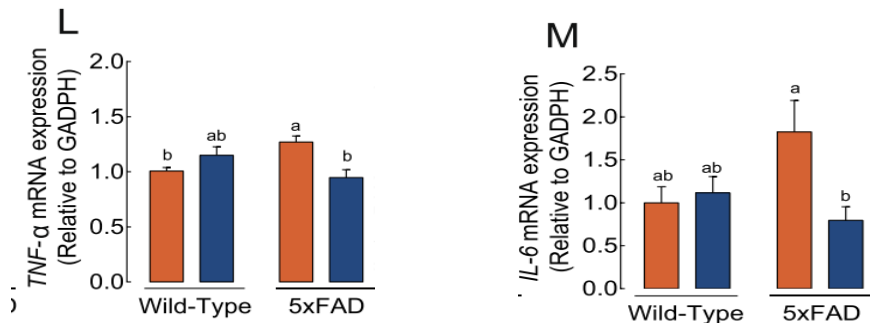
Quantification of Iba-1



IHC Staining of Iba-1



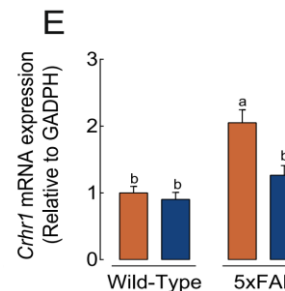
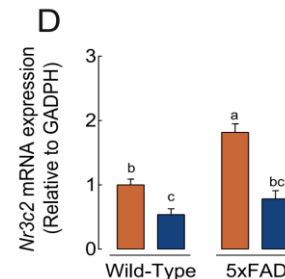
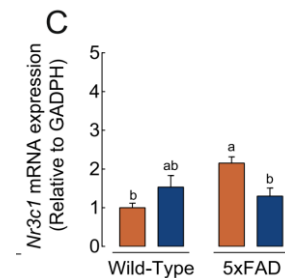
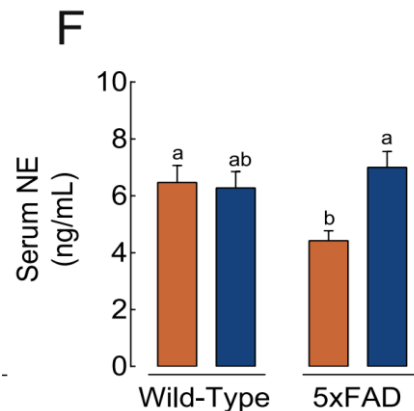
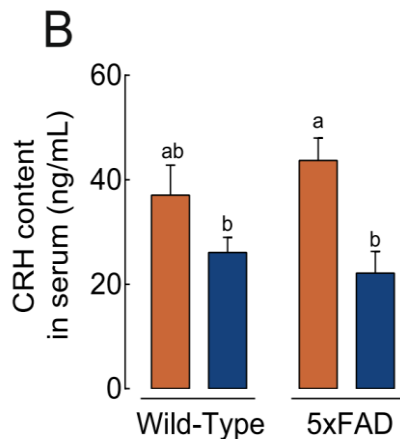
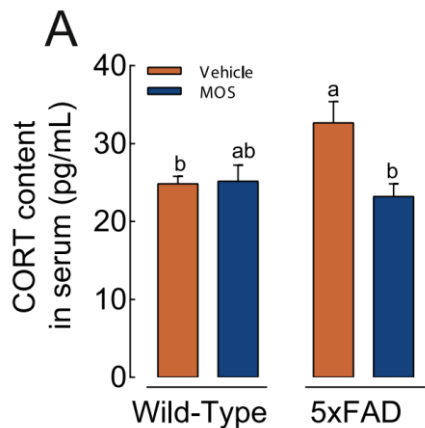
mRNA Expression of TNF- α and IL-6



MOS supplementation effectively alleviated neuroinflammation and oxidative damage in the AD mice brain.

Effects of MOS Treatment Balanced Hormonal Levels of HPA Axis and Monoamine Neurotransmitters Levels 5xFAD Mice.

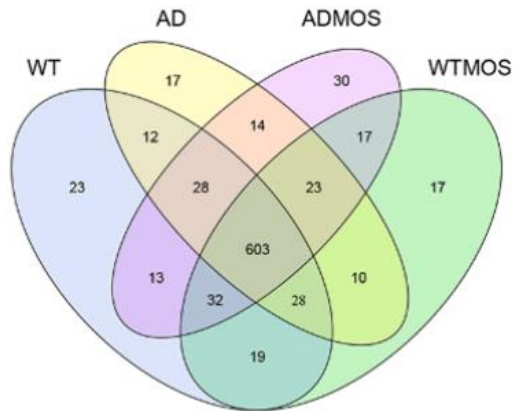
AD mice mitigated the HPA axis hyperactivity, whereas MOS could improve the endocrine function of the HPA and secretion of NE in AD mice.



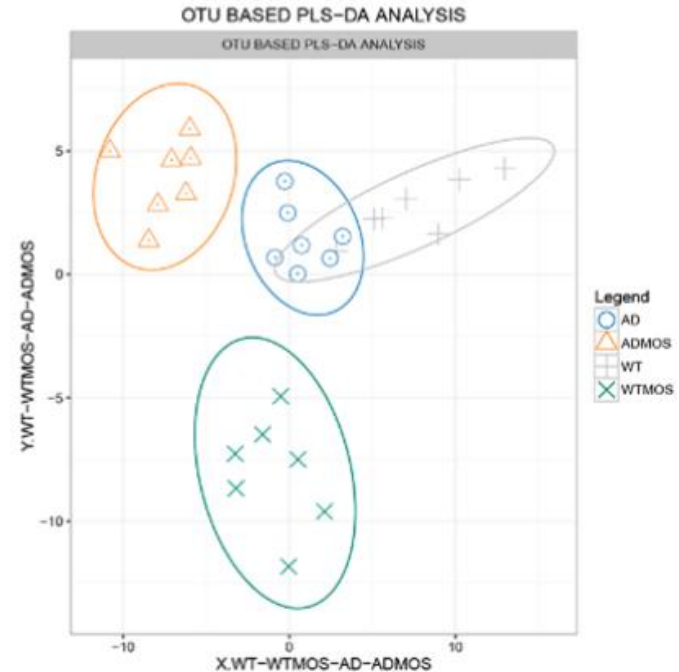
MOS rescued HPA axis activity as indicated by myRNA expression of *Nr3c1*, *Nr3c2* and *Crh1*.

Effects of MOS Treatment on Gut Microbiome Composition and Formation of SCFAs in 5xFAD Mice.

Discrepancy of OTUs in Treatment Groups

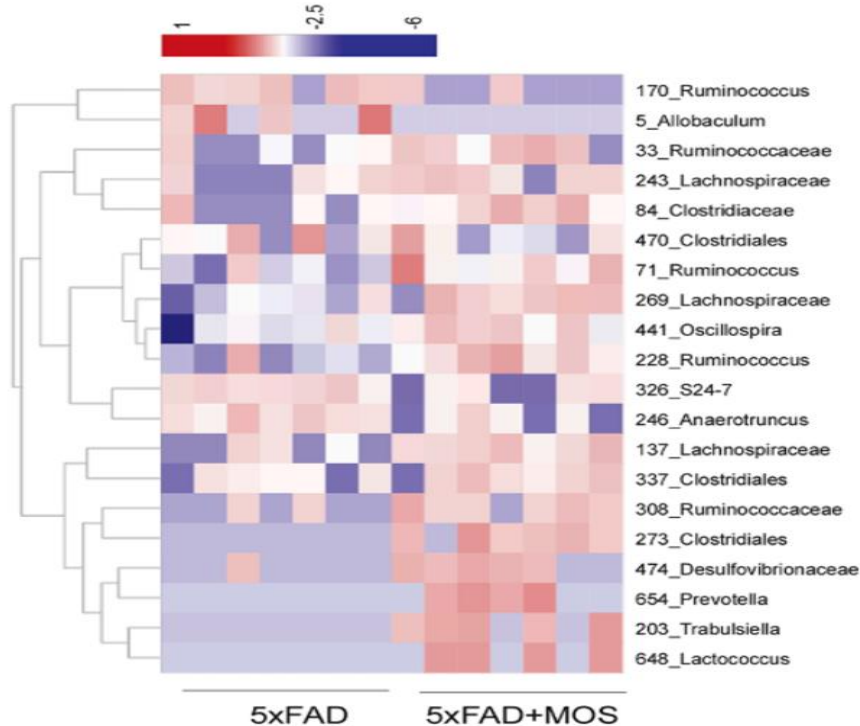


Clustering of OTUs Samples



Effects of MOS Treatment on Gut Microbiome Composition and Formation of SCFAs in 5xFAD Mice ctd.

Gut Microbiota Heatmap

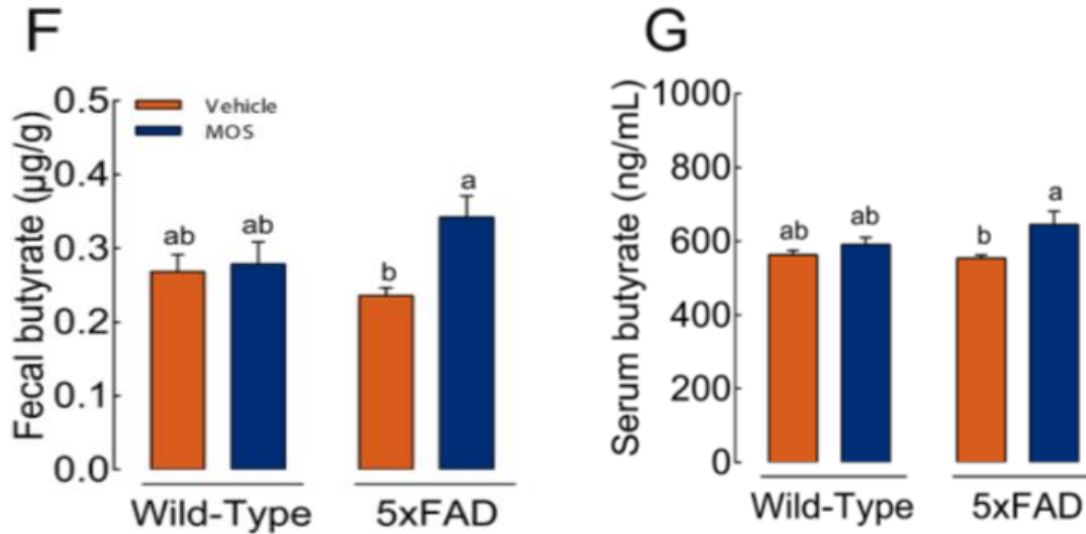


MOS significantly altered the gut microbiome in AD mice.

Effects of MOS Treatment on Gut Microbiome Composition and Formation of SCFAs in 5xFAD Mice ctd.

Letters a - c, $p < 0.05$

Fecal & Serum Levels of Butyrate

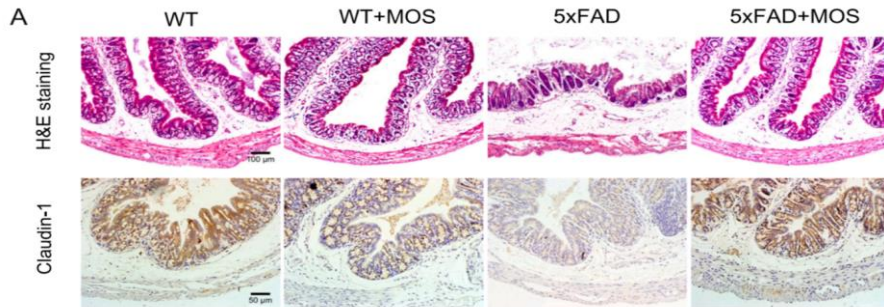


MOS treatment upregulated SCFAs generation and related-microbes enrichment in AD mice gut.

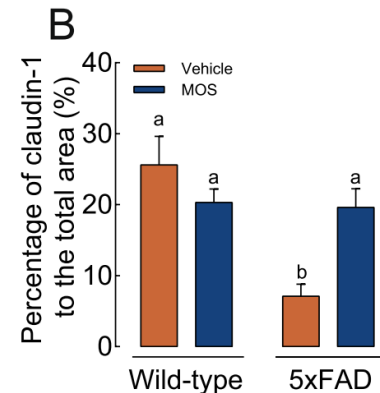
Effects of MOS Treatment on Histopathological Changes and Hormones Secretion of Colon in 5xFAD Mice.

MOS protected the gut barrier integrity in the AD mice.

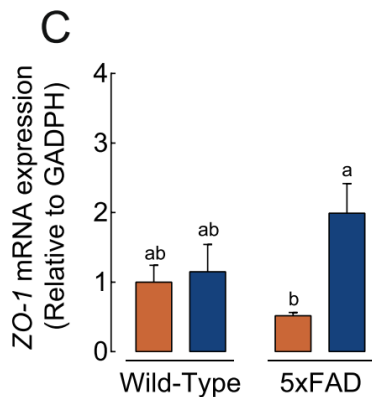
H&E staining and IHC staining of claudin-1 in the colon



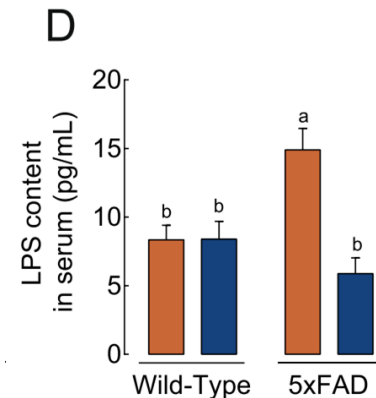
Quantitative immunohistochemical analysis of claudin-1 protein in the colon



The mRNA expression of ZO-1 in the colon



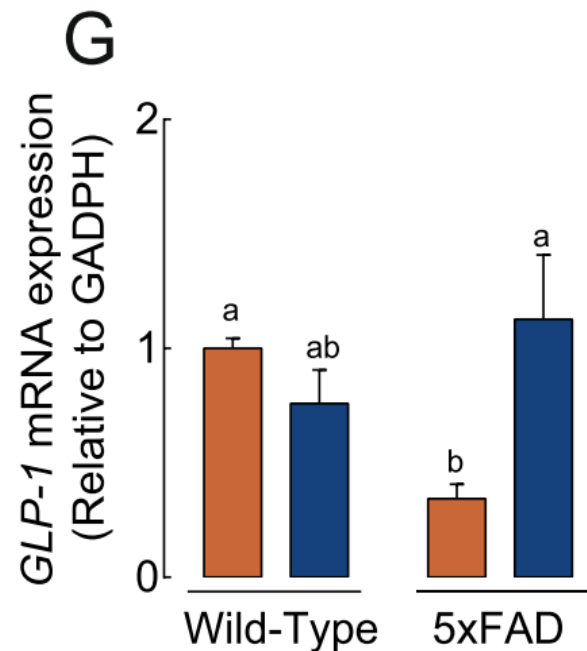
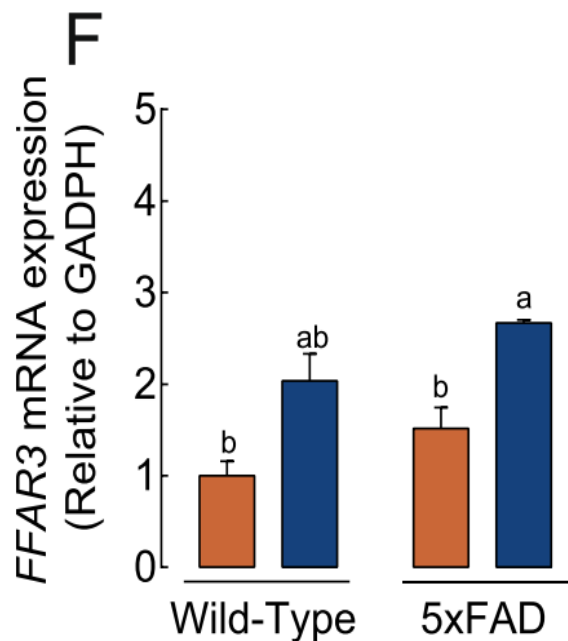
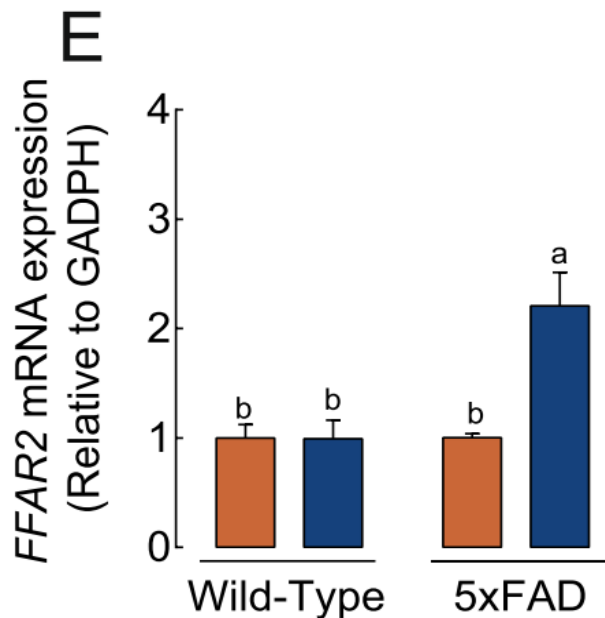
The levels of LPS in the serum



Effects of MOS Treatment on Histopathological Changes and Hormones Secretion of Colon in 5xFAD Mice. (ctd.)

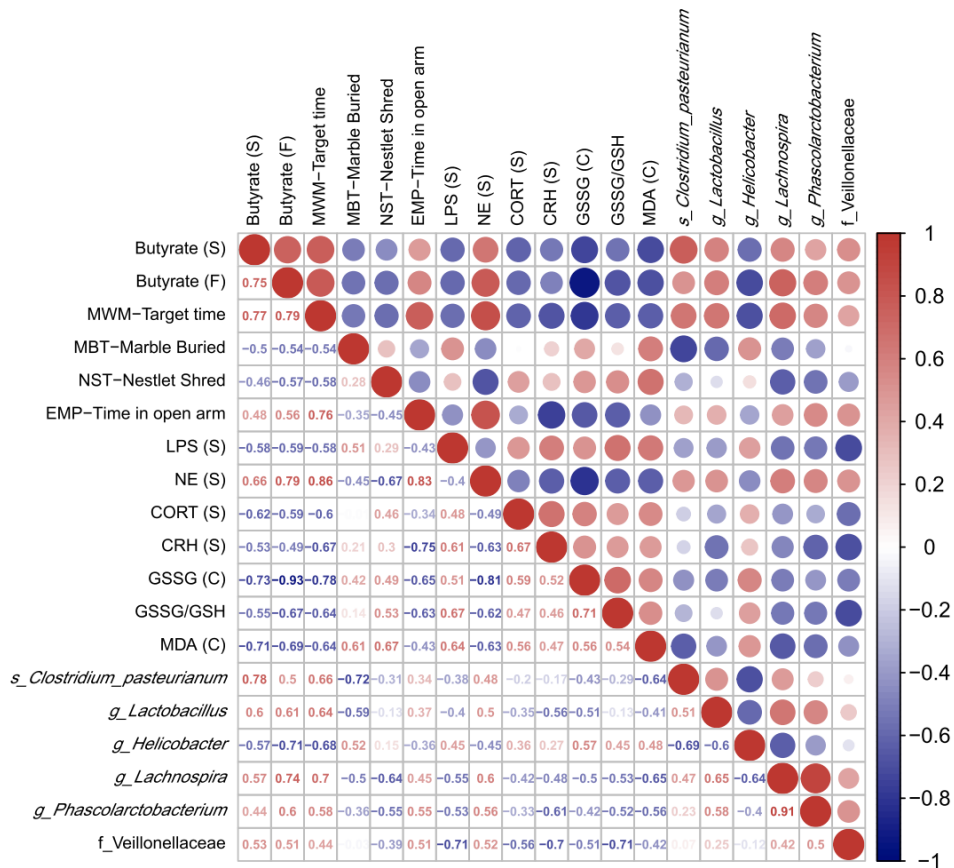
mRNA expression of FFAR2 and FFAR3 mRNA was found to be increased in the colon of MOS- treated AD mice

the treatment of MOS significantly upregulated GLP-1 in AD mice in the colon tissue, compared with the vehicle group



Effects of MOS Treatment on Histopathological Changes and Hormones Secretion of Colon in 5xFAD Mice. (ctd.)

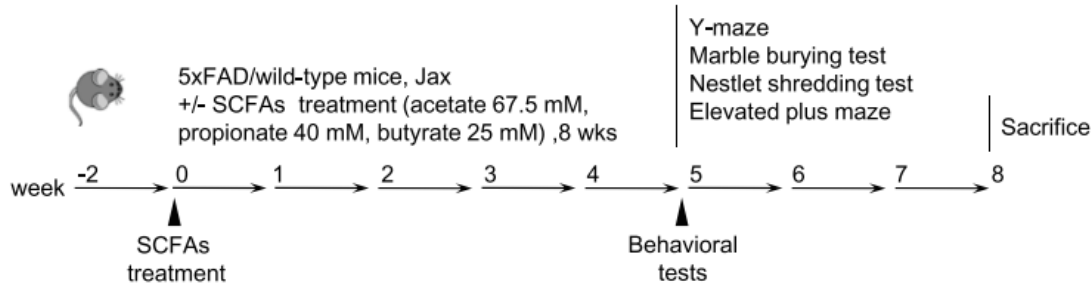
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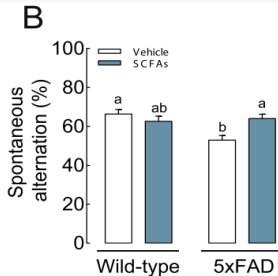
Spearman Correlation Analysis

Effects of SCFAs Treatment on Behaviors and Brain Function in 5xFAD Mice

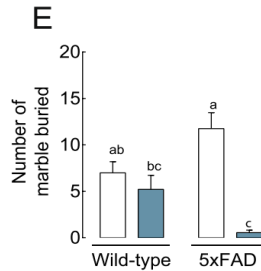
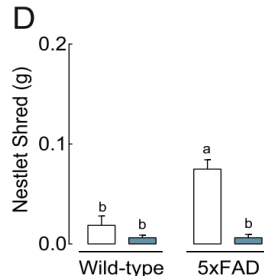
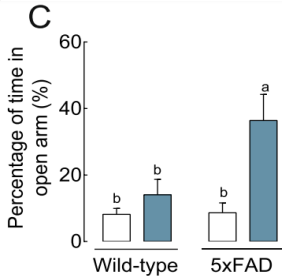
Experimental workflow (n = 8 mice per group)



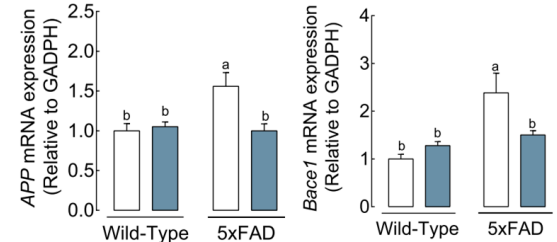
Rescued memory deficits in Y-maze test



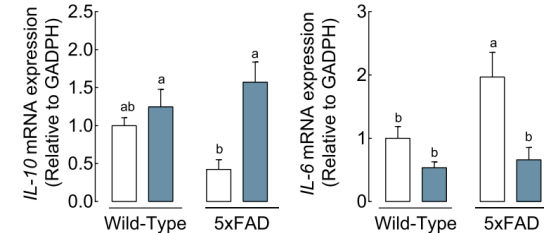
Attenuated anxiety-like behavior



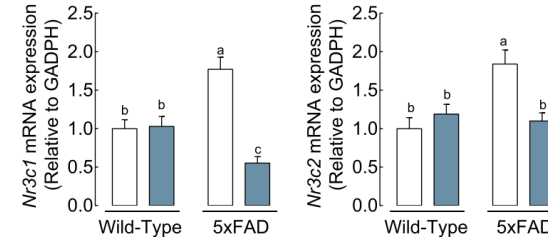
Decreased APP & Bace1 expression

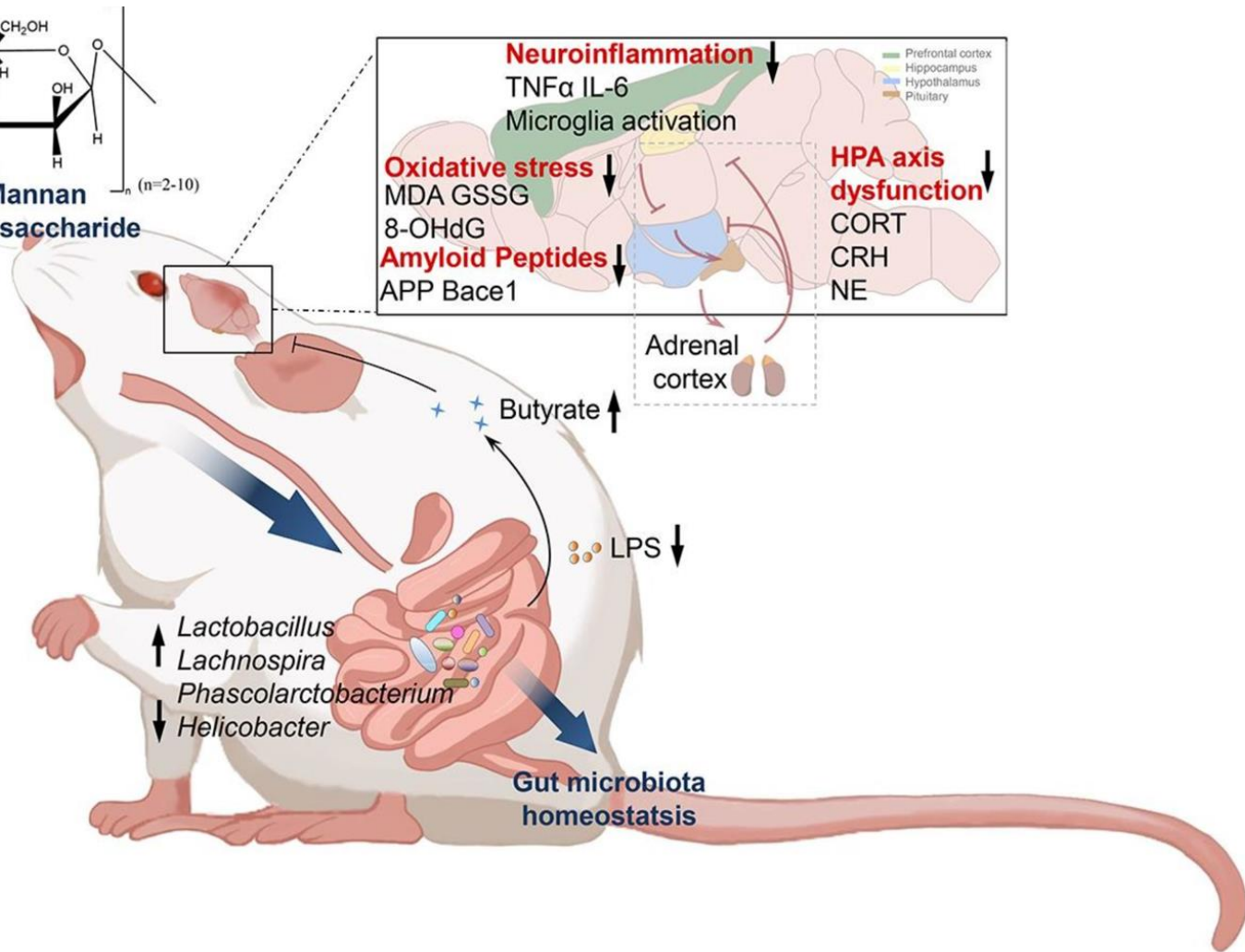
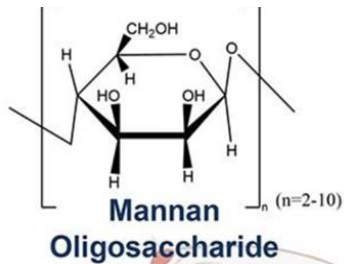


Restored inflammatory responses



Attenuated HPA-axis hyperactivity





Thank You

Any questions?