

# Maternal gut microbiota-derived daidzein prevents osteoporosis in female offspring following prenatal prednisone exposure

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# Introduction

## The DOHaD Theory

The "Developmental Origins of Health and Disease" (DOHaD) theory underscores the long-term impacts of early-life adverse conditions on offspring health and disease susceptibility



## Osteoporosis (OP)

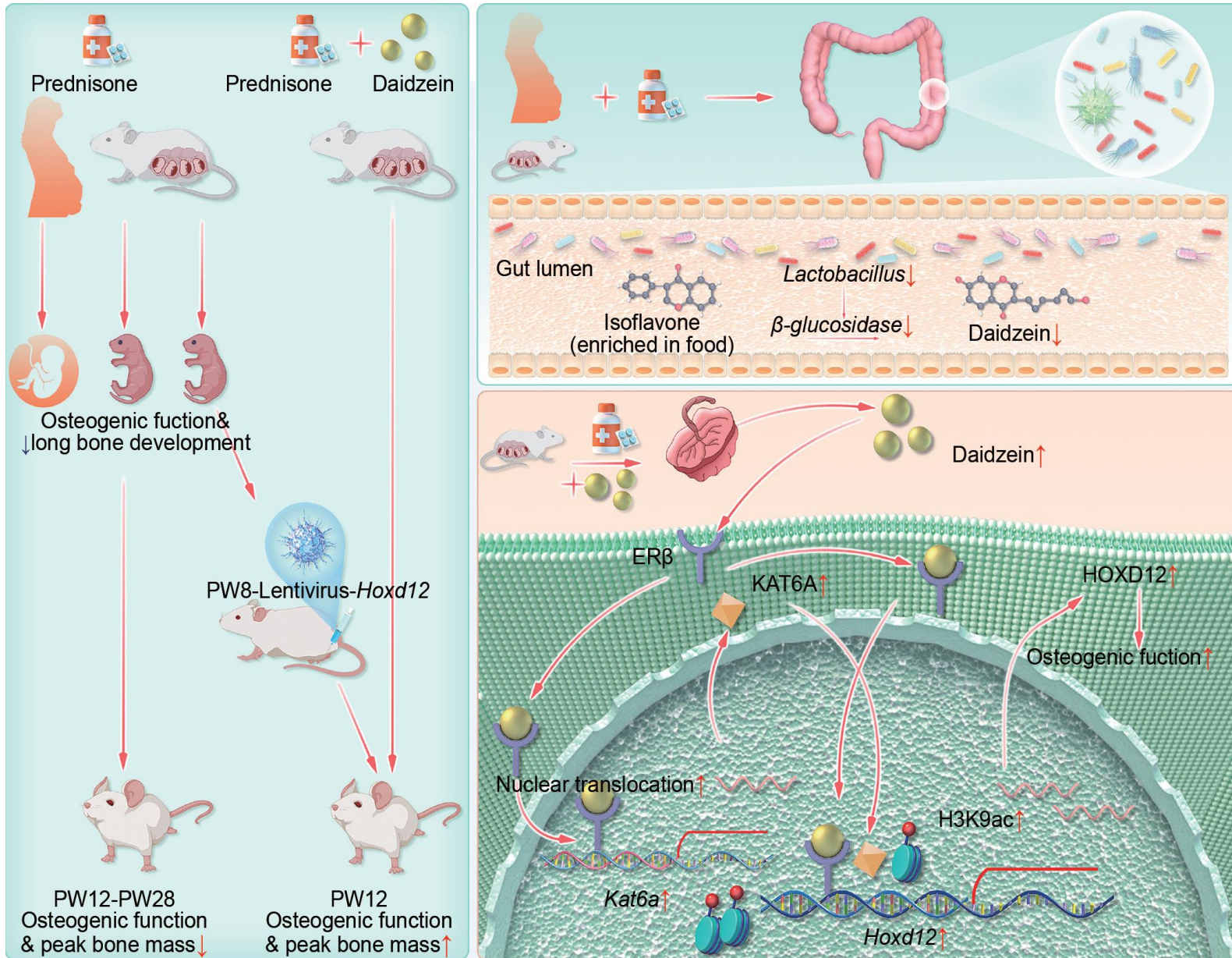
- Characterized by high prevalence and severe clinical consequences
- Pathogenesis remains incompletely elucidated with suboptimal therapeutic efficacy
- Mounting evidence supports its developmental origins during fetal programming

## Prednisone

- Synthetic glucocorticoids
- Administered during pregnancy for managing recurrent miscarriage and rheumatoid arthritis
- Prenatal prednisone therapy (PPT) demonstrates a "double-edged sword" therapeutic paradox
- Prenatal prednisone exposure (PPE) exerts developmental toxicity



# Highlights



1. Prenatal prednisone therapy (PPT)/prenatal prednisone exposure (PPE) induces long bone dysplasia, reduced peak bone mass (PBM), and increased osteoporosis susceptibility in female offspring.
2. Maternal gut microbiota metabolite daidzein (DAI) mediates PPE-induced osteoporosis susceptibility in female adult offspring.
3. DAI mediates the inhibition of osteoblast differentiation and increased susceptibility to osteoporosis in PPE offspring via ER $\beta$ /KAT6A-mediated epigenetic regulation of *Hoxd12* expression.
4. DAI emerges as a target for the early prevention and treatment of PPE-induced multi-organ functional changes and related disease susceptibility.

# Results: PPT induces fetal femoral dysplasia in females and alters maternal gut microbiota composition

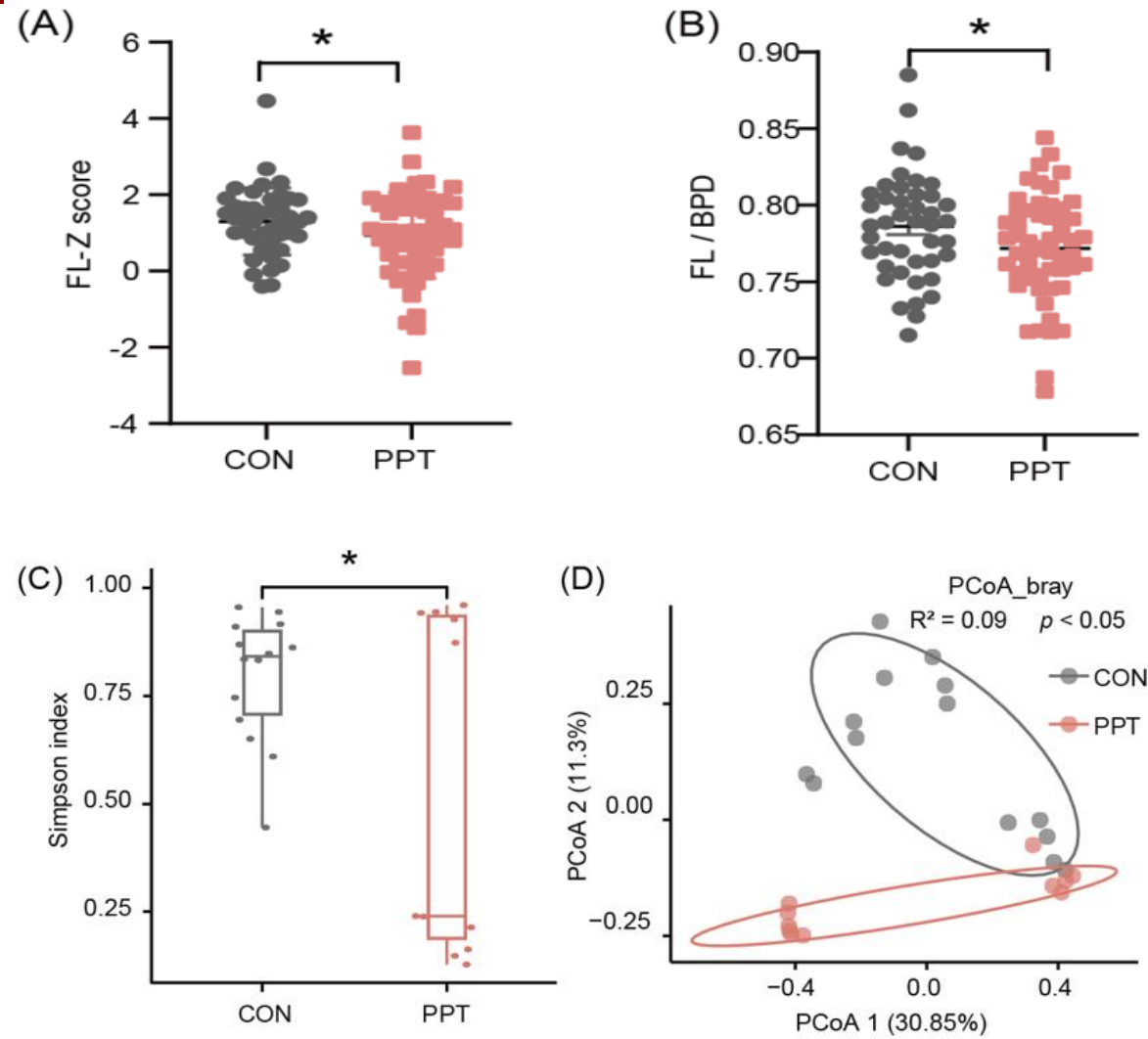


Figure 1A-D: PPT induces fetal femoral dysplasia in female fetuses and alters maternal gut microbiota composition in the human cohort.

# Results: PPE induced alterations in maternal gut microbiota composition and long bone dysplasia in female fetal rats

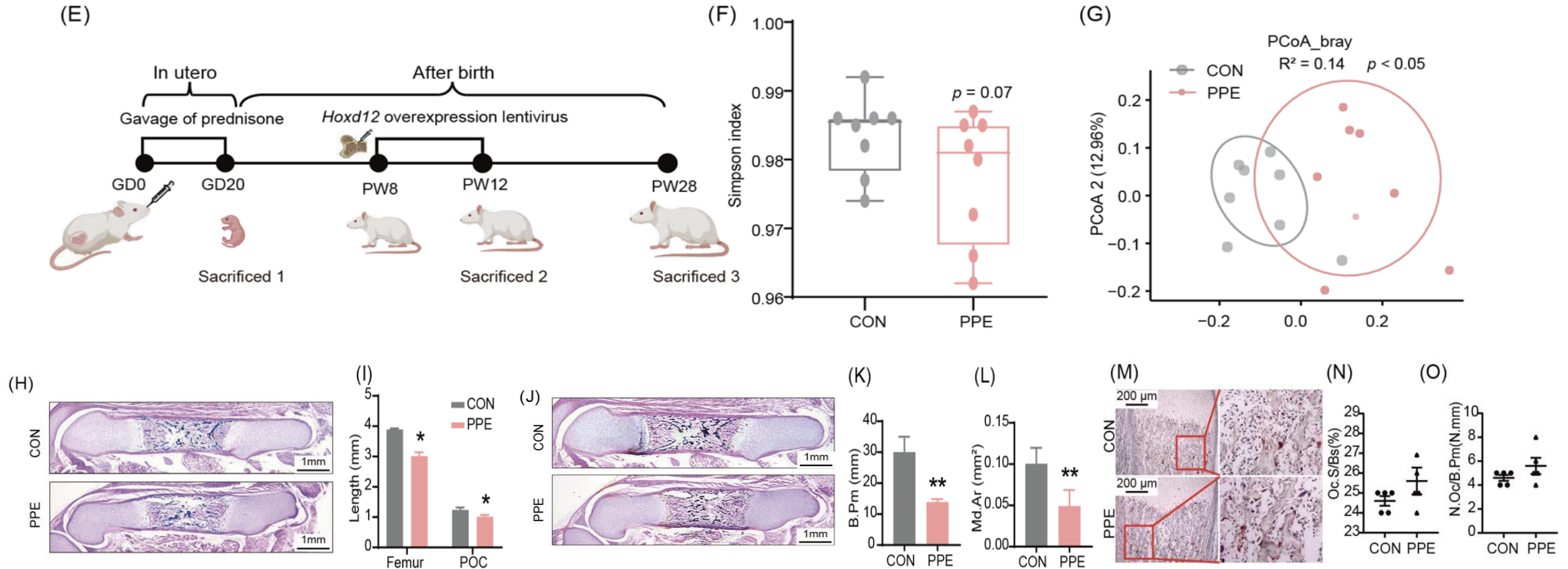


Figure 1E-N: Animal validation studies using a PPE rat model mimicking clinical prednisone dosing regimens demonstrated that PPE induces maternal gut microbiota dysbiosis and causes long bone dysplasia in female fetuses.



# Results: PPE leads to reduced PBM in female offspring rats

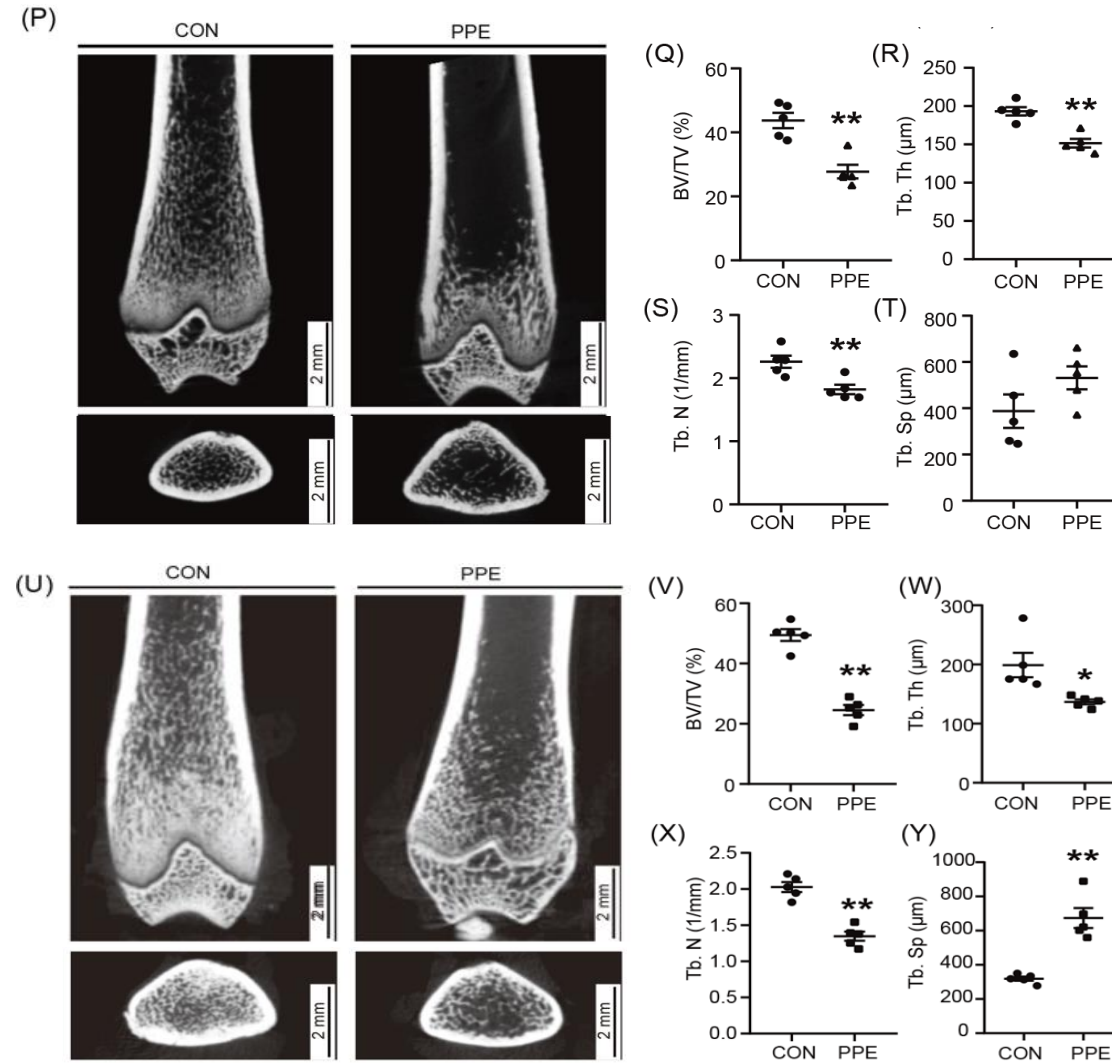


Figure 1P-Y: Analysis of femoral bone mass in female offspring rats at postnatal weeks 12 and 28 revealed that PPE resulted in reduced PBM.

# Results: DAI is an intervention target for osteogenic function and PBM reduction in female offspring rats induced by PPE

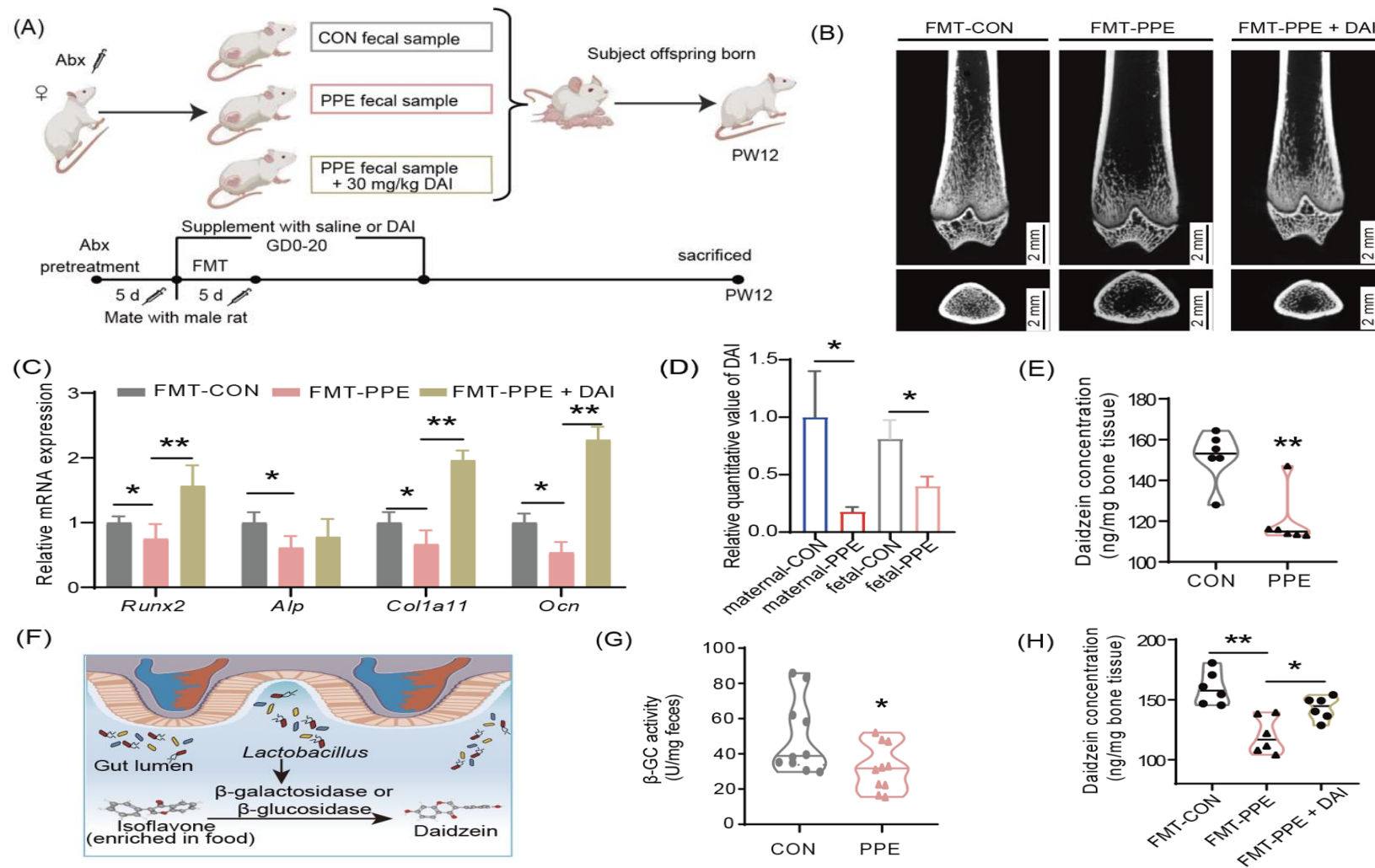


Figure 2A-H: Maternal gut microbiota transplantation experiments demonstrated that gut microbiota dysbiosis induced by PPE mediates the reduction in PBM and impaired osteogenic differentiation in female offspring.

# Results: DAI serves as an effective preventive target against PPE-induced reduction of PBM in female offspring rats

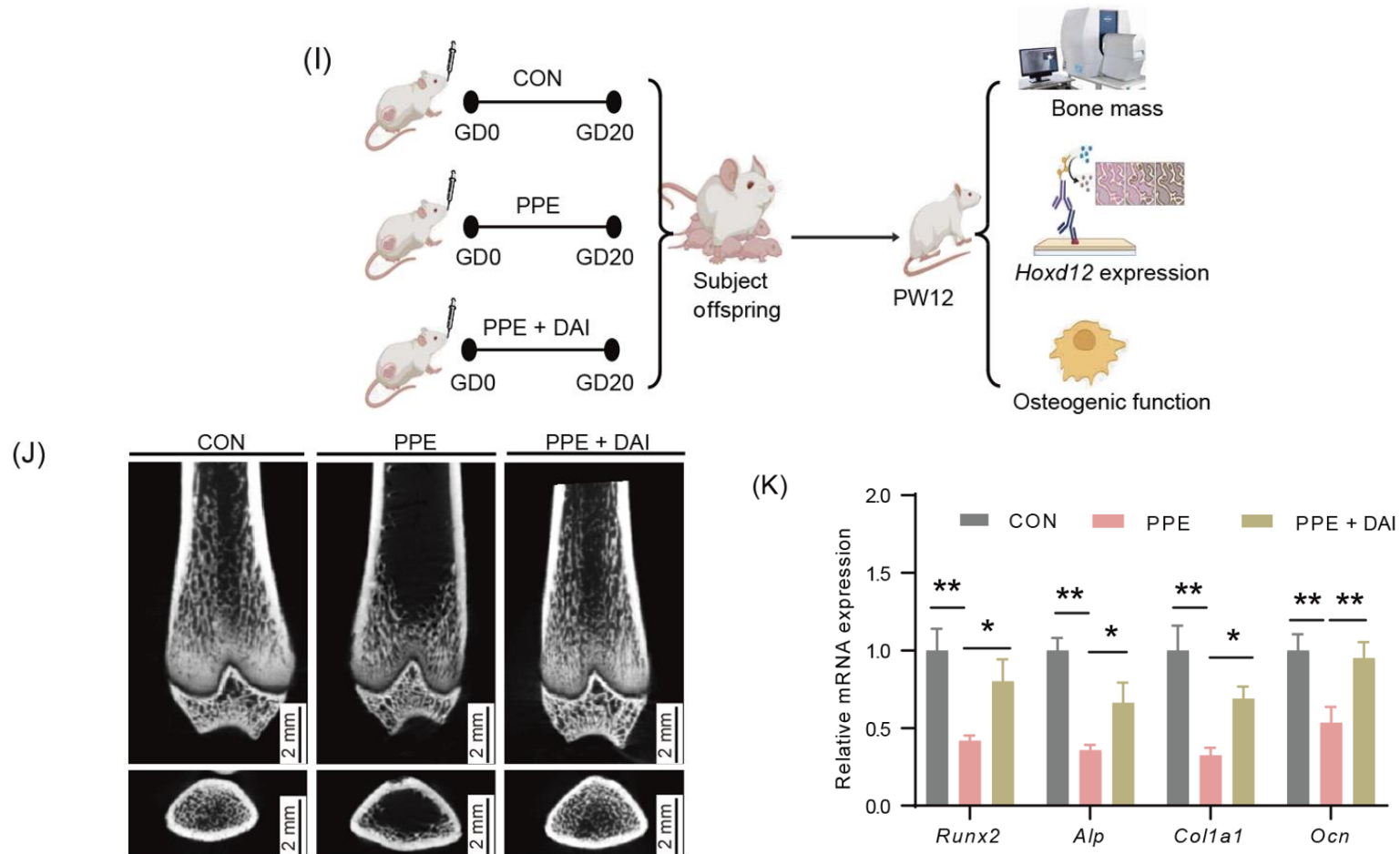


Figure 2I-K: Maternal DAI supplementation during pregnancy significantly reversed PPE-induced reductions in PBM and impaired osteogenic differentiation in female offspring.

# Results: The low expression of Hoxd12 mediated the decrease of PBM in female offspring induced by PPE

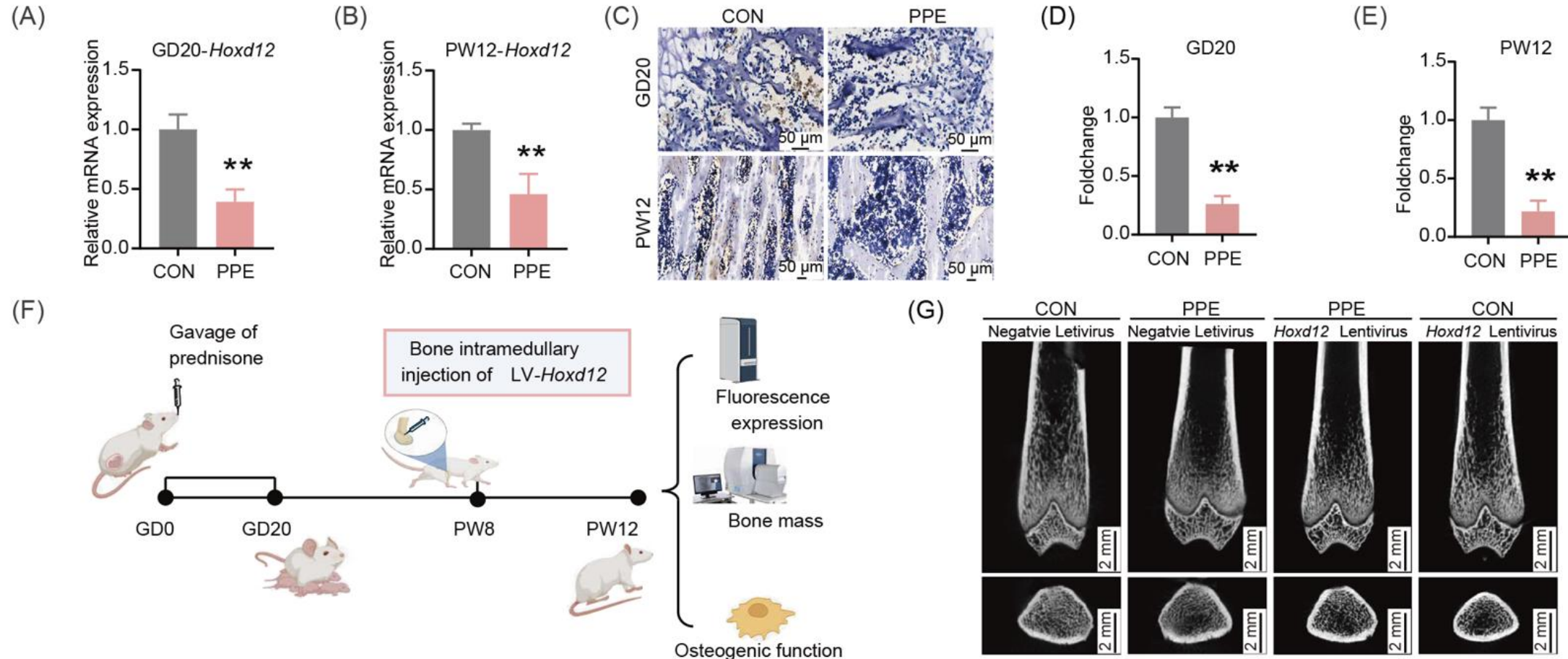


Figure 3A-G: Transcriptomic sequencing of fetal bone tissue combined with postnatal local *Hoxd12* overexpression experiments demonstrated that reduced *Hoxd12* expression mediates PPE-induced PBM suppression in female offspring.

# Results: *Hoxd12* mediates the enhanced osteogenic differentiation of BMSCs in the female offspring of PPE induced by DAI

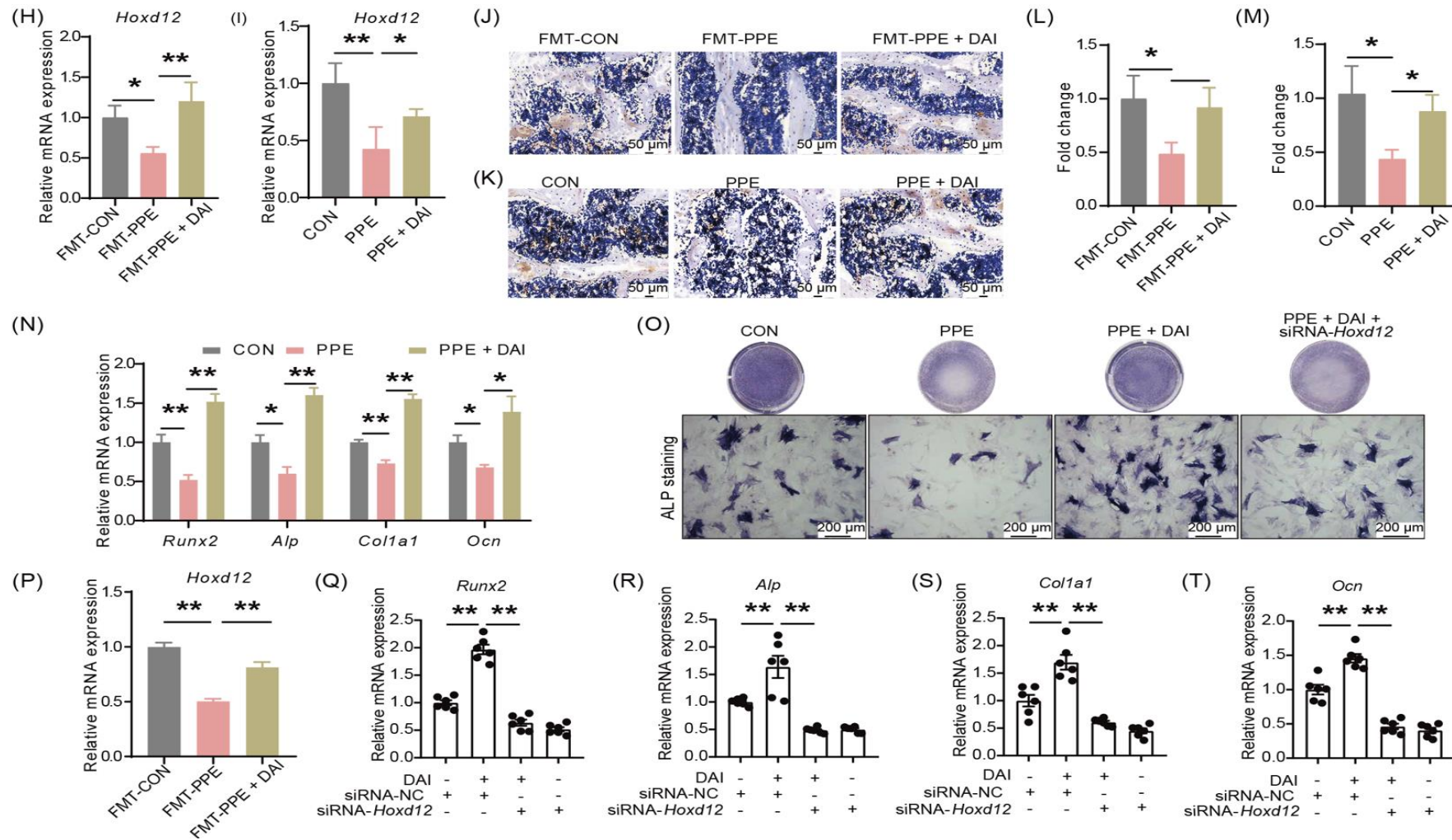


Figure 3H-T: Animal studies demonstrated that DAI reversed PPE-induced downregulation of *Hoxd12* expression. In vitro experiments further revealed that *Hoxd12* mediates the DAI-enhanced osteogenic differentiation of BMSCs derived from PPE-exposed female offspring.

# Results: ER $\beta$ /KAT6A pathway mediates the epigenetic regulation of *Hoxd12* expression by DAI

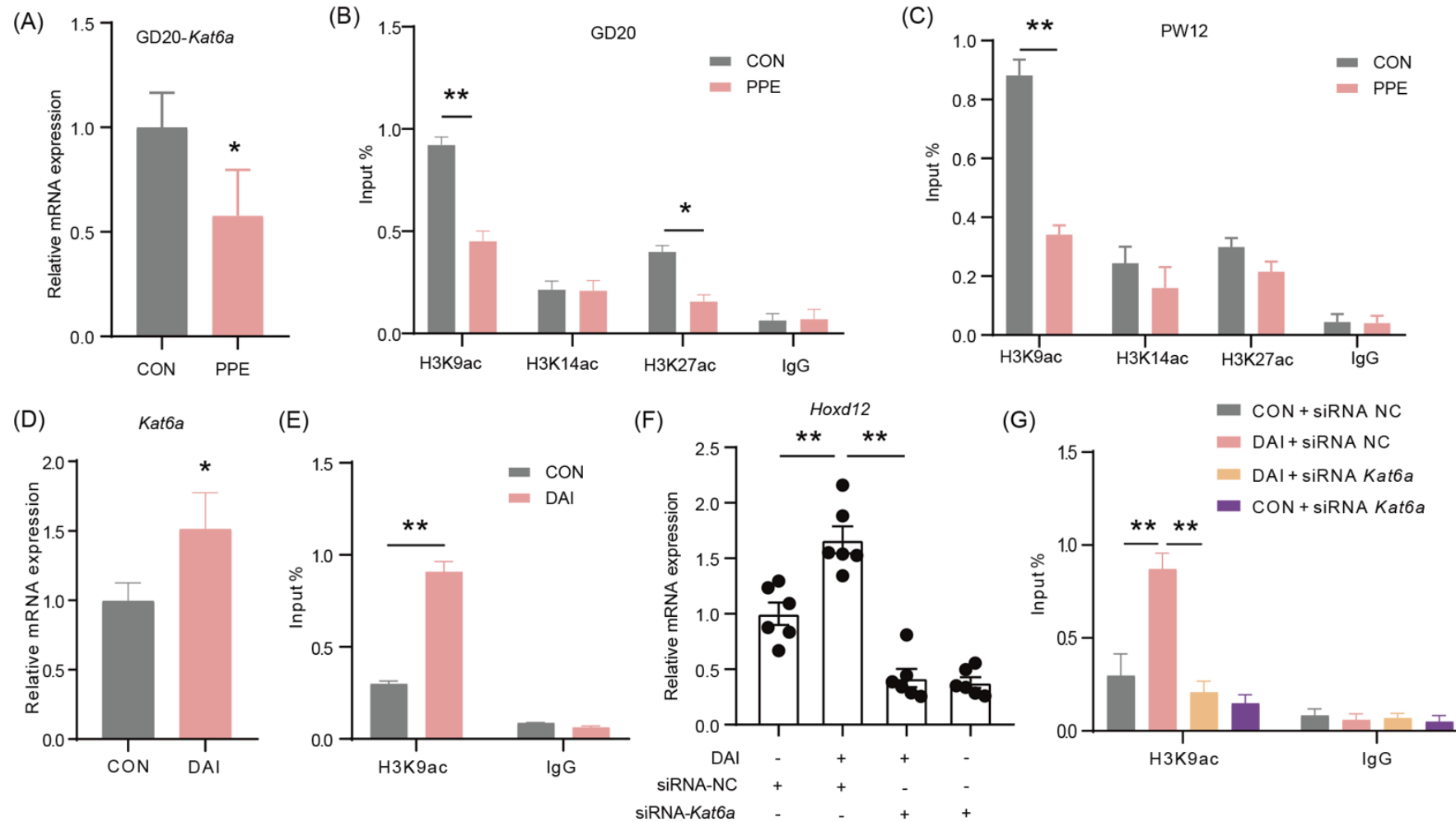


Figure 4A-G: PPE induced persistent reduction of H3K9ac levels at the *Hoxd12* promoter region. In vitro studies further revealed that DAI upregulates *Hoxd12* promoter H3K9ac levels and enhances its transcriptional activity through *kat6a*-dependent mechanisms.

# Results: ER $\beta$ /KAT6A pathway mediates the epigenetic regulation of Hoxd12 expression by DAI

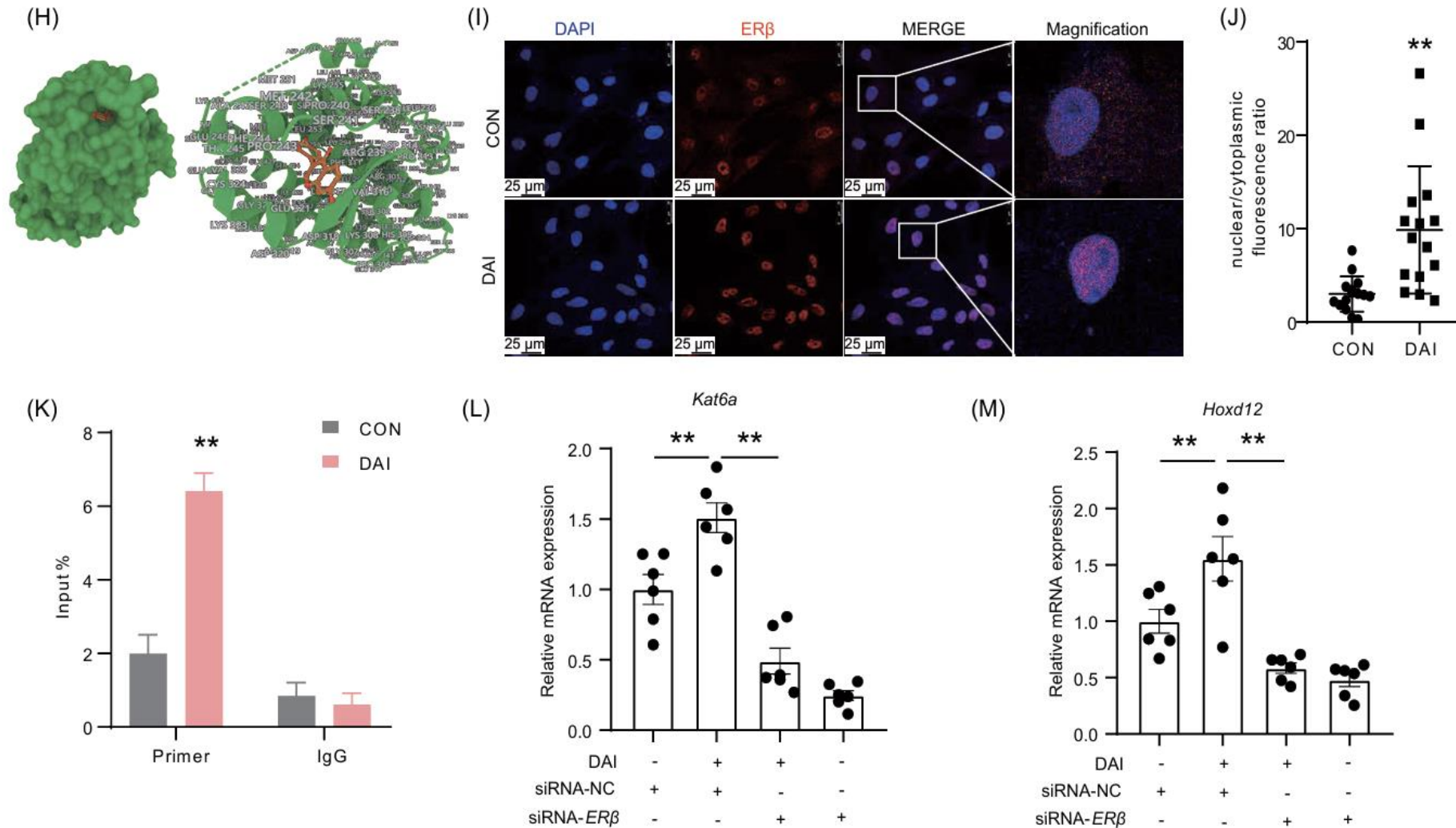


Figure 4H-M: Molecular docking and in vitro experiments demonstrated that DAI promotes *kat6a* expression through ER $\beta$  binding, thereby increasing H3K9ac levels at the *Hoxd12* promoter and enhancing its transcriptional activity.

# Results: ER $\beta$ /KAT6A pathway mediates the epigenetic regulation of Hoxd12 expression by DAI

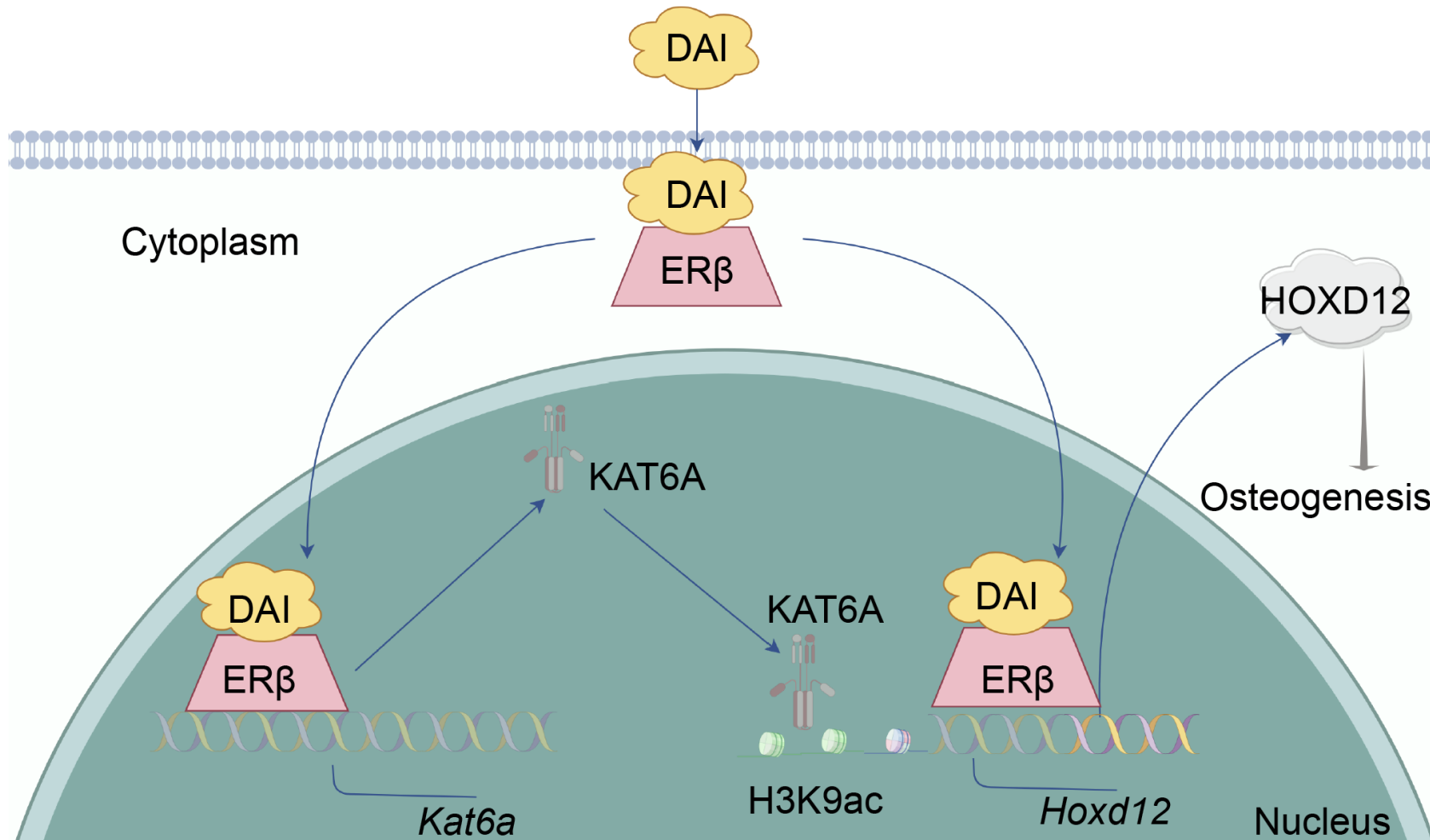


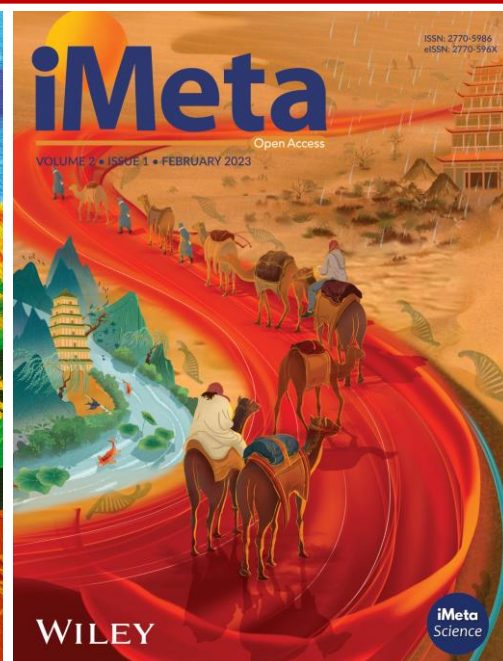
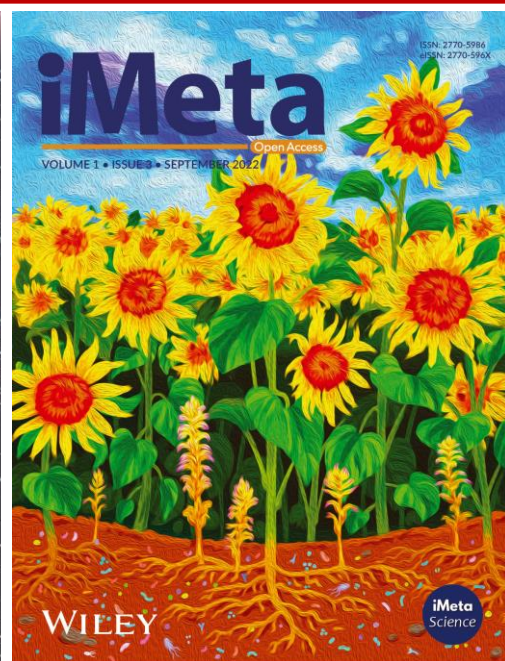
Figure 5: DAI enhances *kat6a* expression via binding to ER $\beta$ , thereby increasing H3K9ac levels at the *Hoxd12* promoter and upregulating its transcriptional activity.



# Summary

1. Clinical investigations revealed that PPT induces maternal gut microbiota dysbiosis and suppresses fetal bone development in female offspring.
2. Animal experiments further demonstrated that PPE causes long bone dysplasia, impaired osteogenic function, reduced PBM, and heightened OP susceptibility in female offspring.
3. Mechanistically, the maternal gut microbiota-derived metabolite DAI mediates PPE-induced long bone dysplasia and PBM reduction in female offspring by ER $\beta$ /Kat6a-dependent epigenetic programming of Hoxd12 expression during prenatal and postnatal osteogenesis.
4. Maternal DAI supplementation during pregnancy reversed PPE-induced: Osteogenic dysfunction, Low PBM, OP susceptibility, and Developmental impairments in multiple organs (liver, hippocampus, adrenal glands, and ovaries)
5. DAI as a novel therapeutic target with translational potential for preventing fetal-origin OP. Furthermore, maternal supplementation of microbiota metabolites emerges as an effective preventive strategy against glucocorticoid-induced fetal developmental programming disorders.

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