

Lepidium meyenii Walp (Maca)-derived extracellular vesicles ameliorate depression by promoting 5-HT synthesis via the modulation of gut–brain axis

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Introduction

Depression is a mental disorder that affects 280 million individuals globally, including 5.0% of adults and 5.7% of the elderly.

Severe depression can lead to suicide, which is the fourth leading cause of death in populations between the ages of 15–29.



Introduction

Lepidium meyenii Walp, also known as Maca, has been cultivated in the Andean region for at least 2000 years and successfully introduced in China since 2002.

In this study, we successfully isolated and purified EVs from Maca (Maca-EVs), and the behavioral tests revealed that Maca-EVs dramatically recovered the depression-like behaviors of unpredictable chronic mild stress (UCMS) mice.



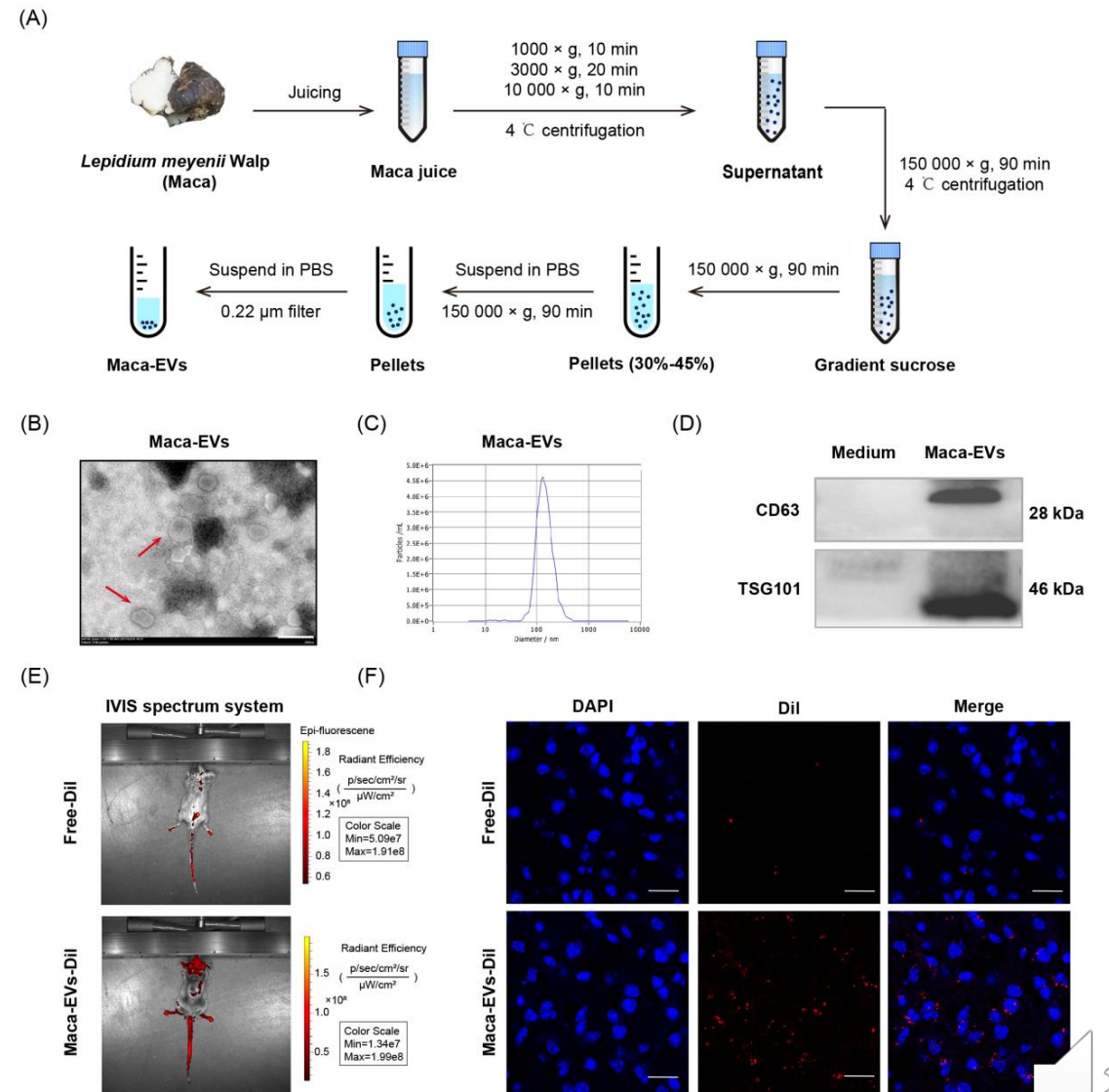
Results

Maca-EVs were isolated from Maca juice using gradient ultracentrifugation.

Transmission electron microscopy imaging and nanoparticle tracking analysis revealed that Maca-EVs were irregular-shaped membrane-enclosed vesicles with an average diameter of 134 nm.

Moreover, Maca-EVs expressed higher EVs markers CD63 and TSG101 than the Maca medium, indicating the successful isolation of EVs from Maca juice.

Figure 1

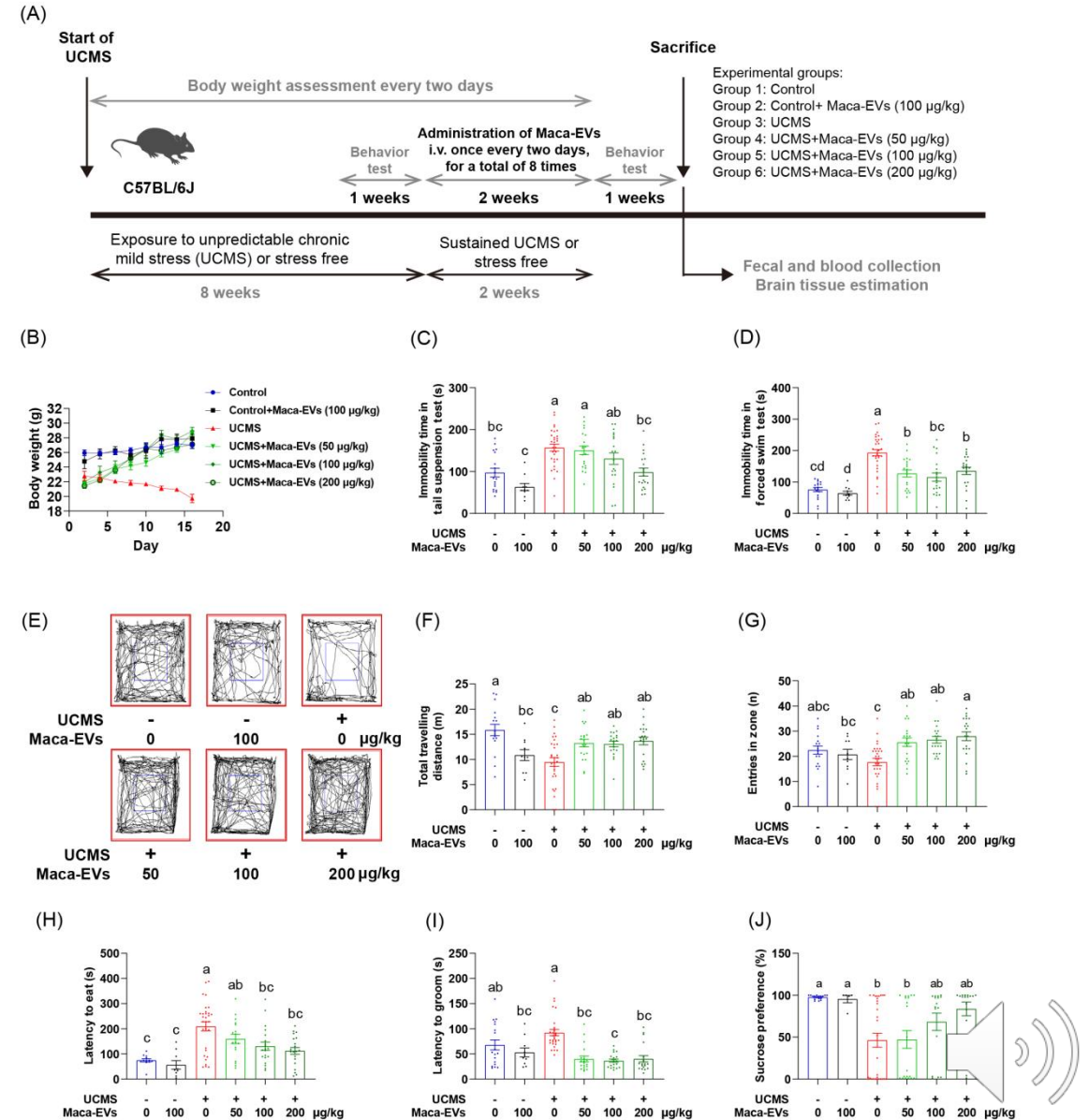


Results

Maca-EVs administration improved depressive-like behaviors in UCMS mice, as shown by the decline in the extended immobility time in the tail suspension test and the forced swim test.

These data suggested the therapeutic potential of Maca-EVs in treating depression.

Figure 2

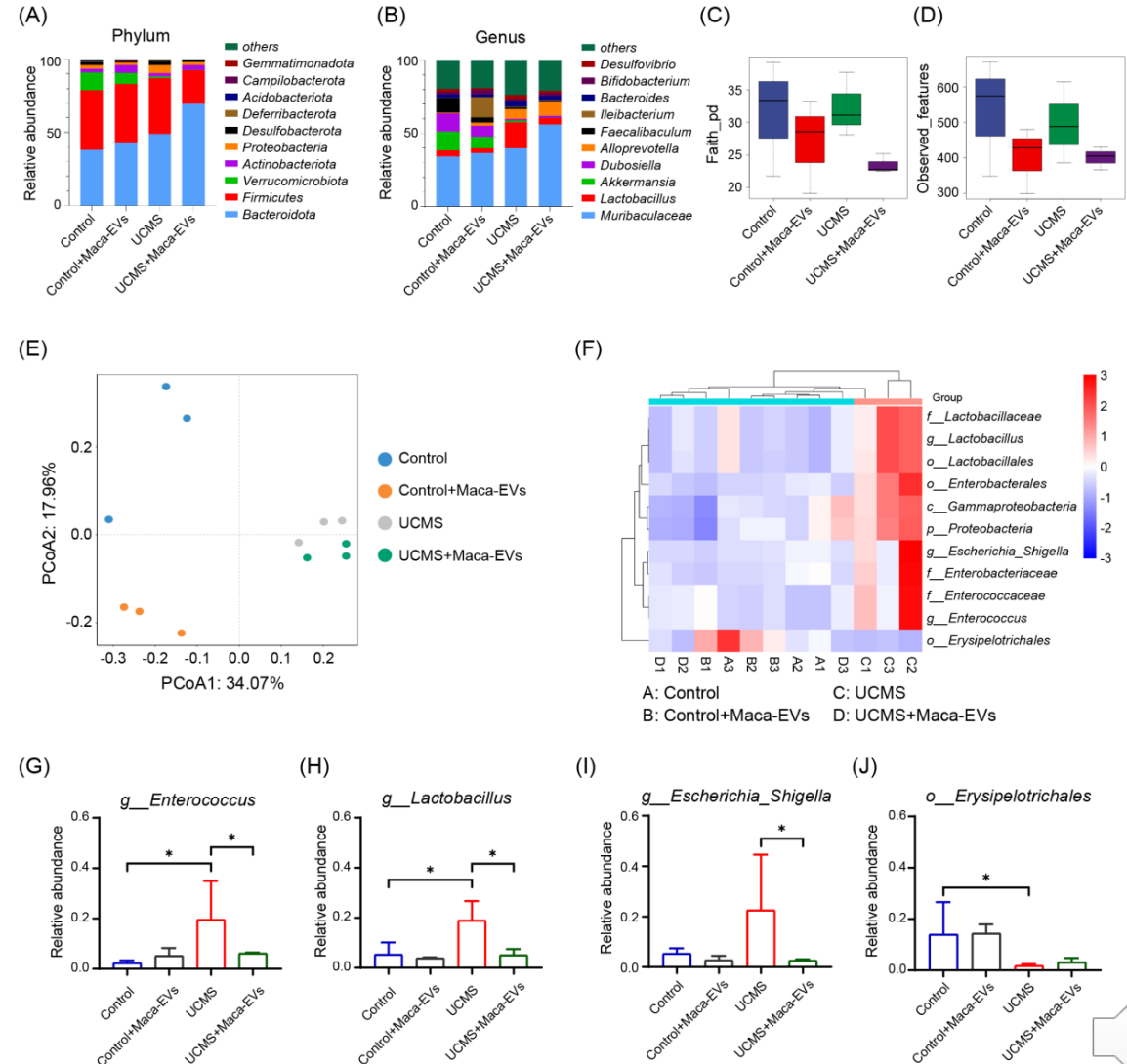


Results

We next investigated the dynamic changes of gut microbiota in mice from across four using 12 fecal samples.

Analysis of the sequencing data indicated that the genera *Lactobacillus*, *Akkermansia*, *Dubosiella*, and *Faecalibaculum* might be associated with the effect of UCMS and Maca-EVs.

Figure 3

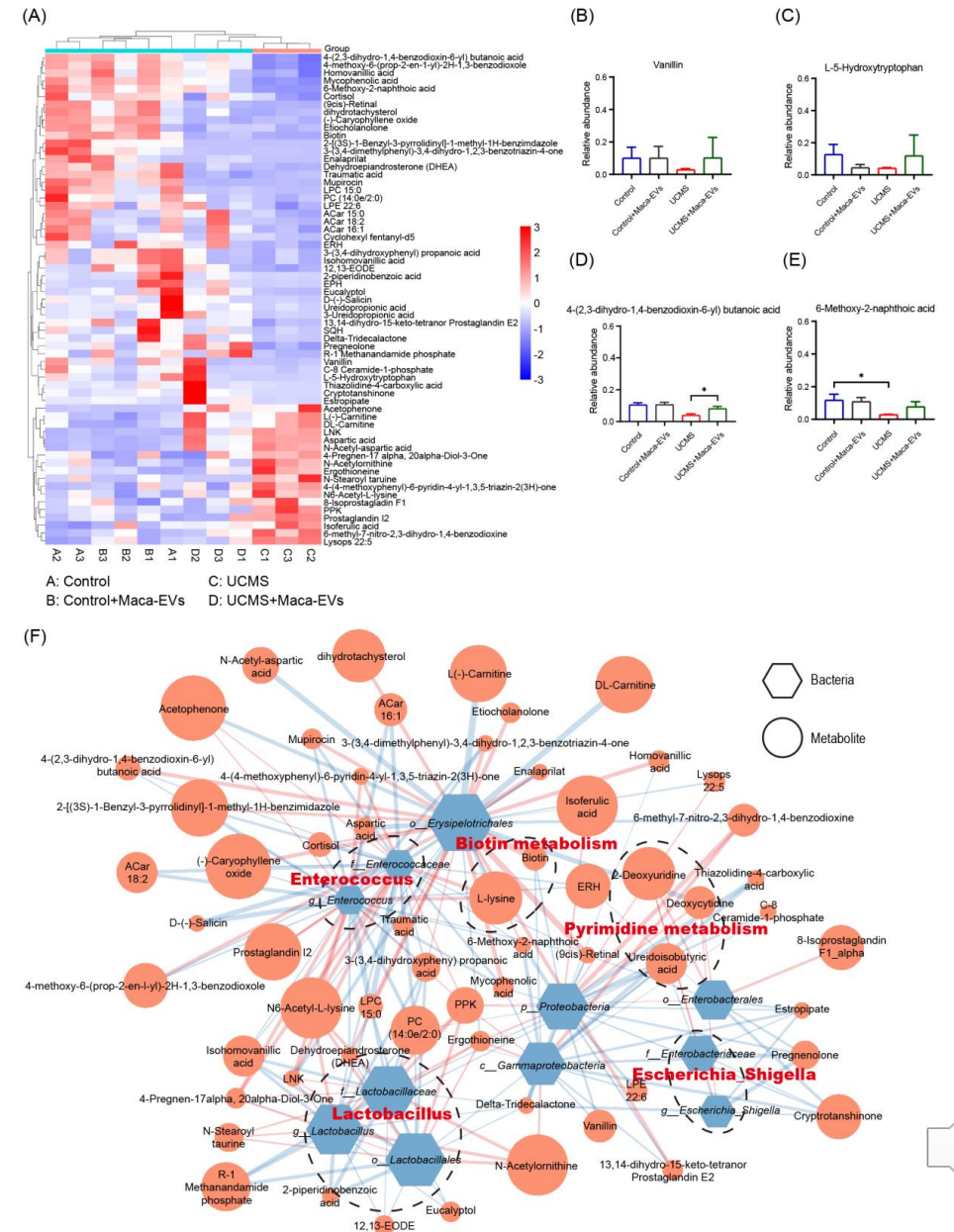


Results

Pathway enrichment analysis indicated that UCMS caused major alterations in metabolic pathway related to biotin, pyrimidine, tyrosine, alanine, aspartate, and glutamate metabolism.

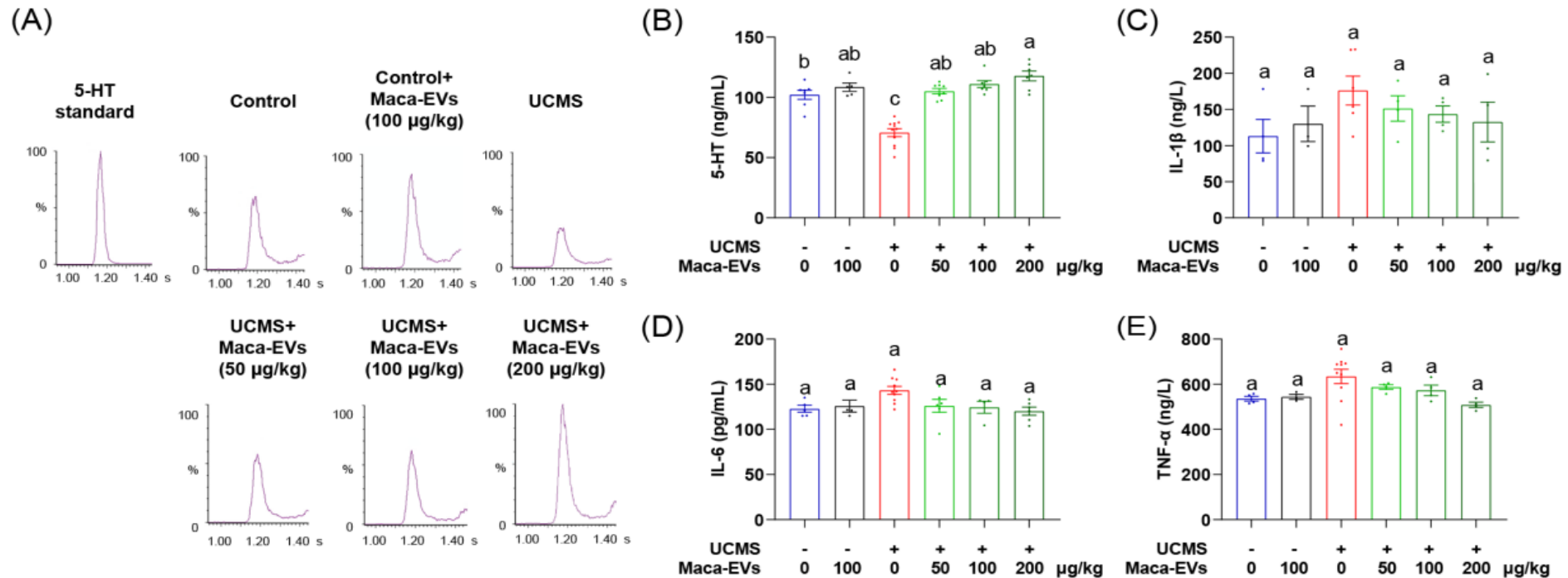
In further metabolomics analysis, we found that the amount of 5-HTP in this pathway was significantly lower in the UCMS group but higher in the UCMS + Maca-EVs group, suggesting that UCMS may affect 5-HT biosynthesis.

Figure 4



Results

Figure 5



Maca-EVs administration dramatically increased serum 5-HT levels in the UCMS model at all doses. The significantly elevated serum NE and DA levels in the UCMS mice were observed when treated with Maca-EVs that started from 100 to 200 µg/kg doses.

Collectively, the serum monoamine neurotransmitters levels, particularly 5-HT, may contribute to the antidepressant effects of Maca-EVs.

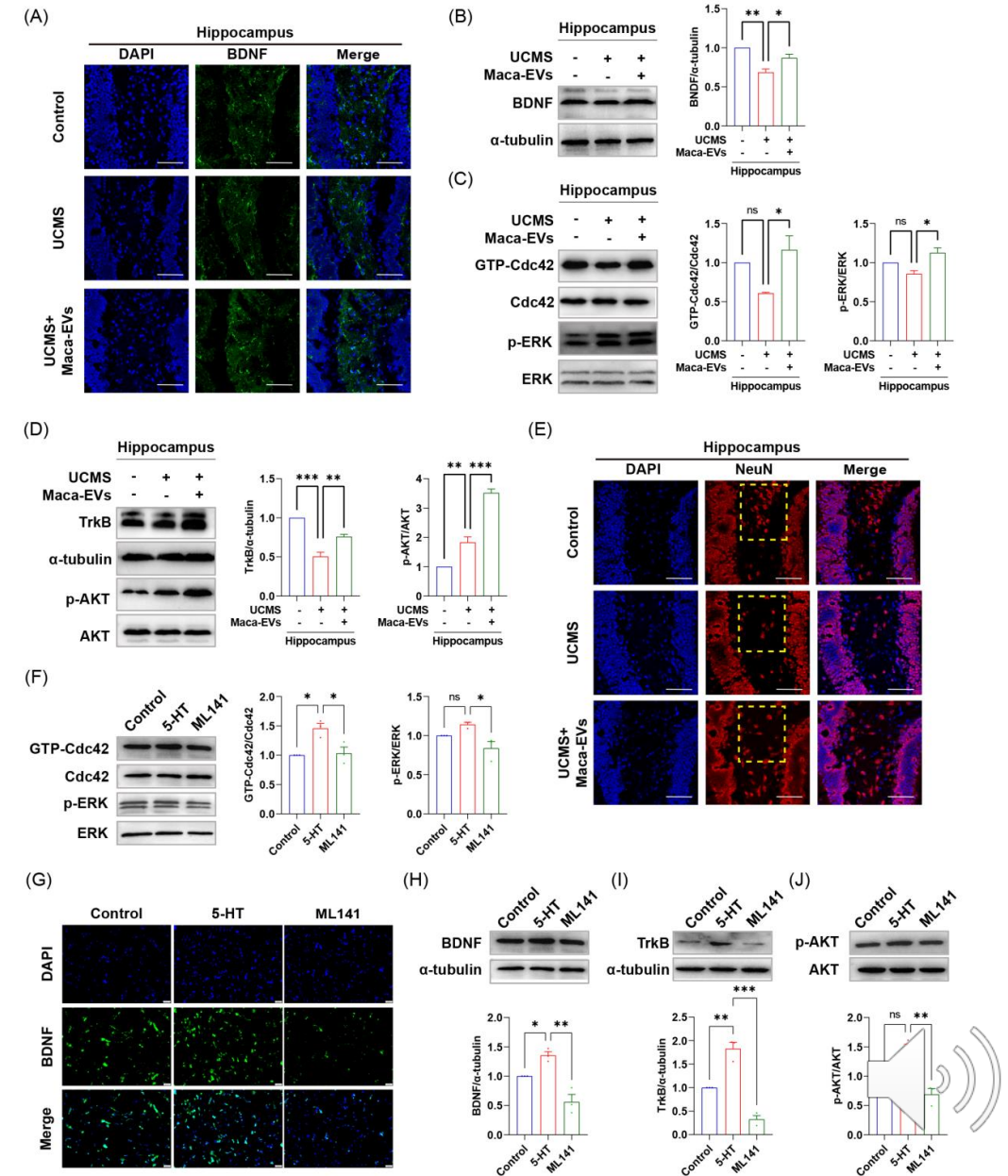


Results

The administration of Maca-EVs at a dose of 200 $\mu\text{g}/\text{kg}$ significantly increased serum 5-HT levels, promoting us to investigate whether it would enhance BDNF expression in the UCMS mice.

Our data suggest that Maca-EVs attenuate the decrease in BDNF expression by triggering the GTP-Cdc42/ERK signaling in the hippocampus and cortex of UCMS mice.

Figure 6

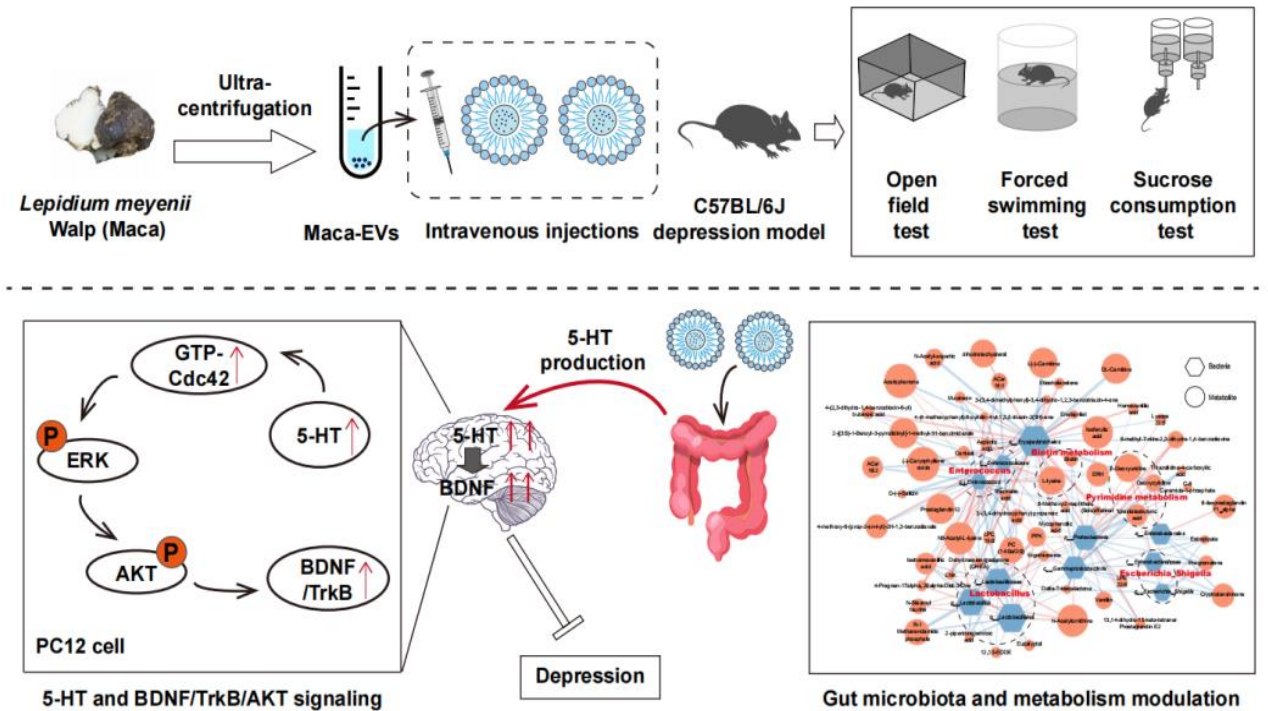


Summary

This study reports the isolation and characterization of Maca-EVs, which exhibit antidepressant effects in UCMS mice.

These effects were accompanied by alteration in depression-related fecal microbiota and enhanced gut 5-HT metabolism, as well as elevated serum 5-HT concentrations.

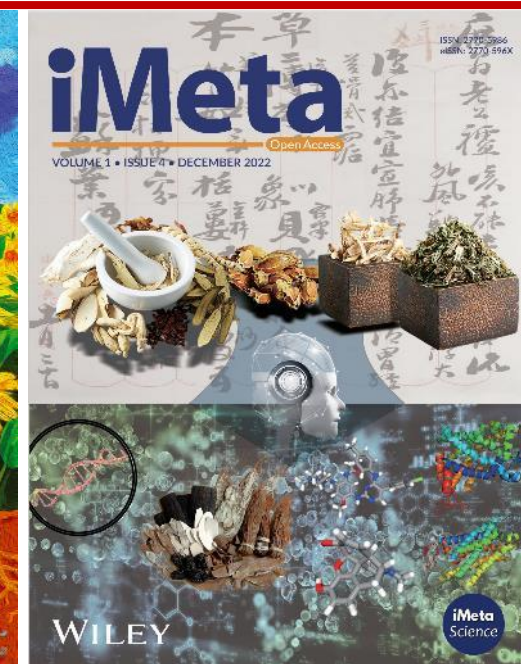
Further studies are required to evaluate the safety and efficacy of this approach.



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