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ORIGINAL RESEARCH

Tellimagrandin II Stimulates Inflammasomes by Causing an Accumulation of 3-Aminopropanal, Which Promotes Apoptosis of Endometriotic Cells While Inhibiting Invasion

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Background: Endometriosis is frequently treated with Paeoniae Radix. It contains Tellimagrandin II, which has the role of modulating immunity and anti-tumor. Therefore, we will explore the effects of Tellimagrandin II on the apoptosis and invasion/migration of ectopic endometrial cells (EECs).

Methods: Tellimagrandin II was used to treat EECs, and transcriptomics and bioinformatics techniques were used to identify its main pathways and targets of Tellimagrandin II. Western blotting was used to confirm the expression of essential targets. Flow cytometry was applied, the impact of tellimagrandin II on EECs apoptosis was identified. Transwell assays were conducted the effects of Tellimagrandin II on EECs invasion and migration. Finally, the binding of tellimagrandin II to key targets was confirmed using molecular docking techniques.

Results: Tellimagrandin II may inhibit pathways like beta-alanine metabolism and ECM-receptor interaction while activating JAK-STAT, NF-κB, and apoptotic pathways, according to transcriptomics and GSEA enrichment analysis. Tellimagrandin II can inhibit ALDH7A1 expression in EECs as well as increase SMOX expression, which may facilitate the accumulation of 3-Aminopropanal. This action becomes more pronounced as the dosage is increased. By upregulating the expression of NLRP3, TIMP-1, Caspase-3, BAX, and Caspase-1 in EECs while decreasing the expression of β-catenin and MMP2, tellimagrandin II can prevent EECs invasion and migration and encourage EECs apoptosis. Tellimagrandin II exhibited good docking with ALDH7A1 and SMOX, according to molecular docking.

Conclusion: Tellimagrandin II may stimulate inflammasomes by encouraging 3-aminopropanal accumulation within EECs. The increase in inflammasomes may promote EECs apoptosis and inhibit EECs invasion and migration. However, its in vivo inhibitory effects on endometriosis require further investigation.

Keywords: tellimagrandin II, 3-aminopropanal, inflammasome, endometriosis apoptosis, invasion

Introduction

In obstetrics and gynecology, endometriosis is a frequent condition that can produce symptoms including infertility, anxiety, and depression in patients.[1] When it comes to treating endometriosis, traditional Chinese medicine offers several benefits, including minimal side effects, and long-lasting results. However, elucidating the precise mechanism of disease treatment is challenging due to the complexity of the components in herbal. Therefore, identifying essential ingredients in herbal that effectively treat endometriosis is crucial. Finding essential ingredients in Herbal that effectively treat endometriosis is therefore crucial. Paeoniae Radix is very effective at reducing pain and increasing blood flow. It is frequently used in traditional Chinese medicine to treat endometriosis. It can be found in several conventional prescriptions for female abdominal pain, including Danggui Shaoyao Powder, Guizhi Fuling Pills, and Shaoyao Gancao

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Decoction,[2],[3,4] Tellimagrandin II, which is produced from shaoyao, has antibacterial, immune-regulating, and tumor cell apoptosis-promoting properties,[5],[6–8] Since endometriosis shares traits with tumors and is characterized by immunological abnormalities and inflammation, this article will examine how Tellimagrandin II affects ectopic endometrial cells (EECs) to set the stage for further research.

Materials and Methods

Experimental Reagents and Instrument

Tellimagrandin II (Yongjian: B02179), Spermine Oxidase (SMOX) Polyclonal antibody (proteintech: 15052-1-AP), Aldehyde Dehydrogenase 7A1 (ALDH7A1) Polyclonal antibody (proteintech: 10368-1-AP), Anti-NLR Family, Pyrin Domain Containing Protein 3 (NLRP3) Rabbit pAb (Servicebio: GB114320-50), Recombinant Anti-beta Catenin (β-Catenin) antibody (Servicebio: GB150016-100), Anti-Matrix Metallopeptidase 2 (MMP2) Rabbit pAb (Servicebio: GB11130-100), Anti- Tissue Inhibitors of Metalloproteinase 1 (TIMP1) Rabbit pAb (proteintech: 16644-1-AP), Anti-Caspase-3 Rabbit pAb (Servicebio: GB115600-100), Anti-Bcl-2-associated X(Bax) Rabbit pAb (Servicebio: GB11690-100), Anti-Caspase-1 Rabbit pAb (Servicebio: GB11383-100), DMEM/F12 (Glutamine and HEPES)(M&C GENE: CM10092), Fetal Bovine Serum Gold (YEASEN: 40130ES76), penicillin streptomycin mixture (Servicebio: P1400), 1×PBS buffer (Solarbio: P1020), trypsin-EDTA digestion solution (Phenol Red)(Solarbio: T1320), CCK-8 kit (Sola rbio: CA1210), Annexin V-FITC Apoptosis detection kit (Beyotime: C1062S), 96-well cell culture plate (Servicebio:) CCP-96H, SWE matrix adhesive (Solarbio: G4131-5ML), crystal violet staining solution (Solarbio: G1014-50ML), paraformaldehyde fixative (Solarbio: G1101-500ML), Transwell chamber (Corning: WG3422) Cell culture flasks (Corning: 430639), 12Z EECs line (Bioharbor: LH-H337), DMSO (Servicebio: GC203006-10mL), Propidium Iodide (proteintech: CM18819), Flow cytometer (BD: FACSAria II), Gel imaging system (Alpha: 2200) Electrophoresis apparatus (Thermo: EC250-90), Thermo Corporation, USA; Pendulum type decolorizing shaker (model: DS-2S100), Nanodrop micro spectrophotometer (Illumina: Nanodrop2000), sequencing platform machine (Illumina: NovaSeq X Plus).

Cell Culture

The 12Z EECs line is derived from the lesions of patients with endometriosis.[9] It can adhere to and proliferate on surfaces, exhibiting stable properties and a passage interval of 2–3 days. Currently, it is widely utilized in various endometriosis-related studies. In a 37°C, 5% CO_2 incubator, EECs were cultured in a DMEM/F12 medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin. These cells adhere to the culture surface and resemble epithelial cells. Following a 1:2 passage, they can achieve maximum growth within 2 days and exhibit a typical diploid karyotype. With no signs of tumorigenicity were observed. In the experiment, we utilized passages 8–10 of EECs.

CCK8 Experiment

Prepare six medication concentrations of 0 μg/mL, 5 μg/mL, 25 μg/mL, 50 μg/mL, 75 μg/mL, and 100 μg/mL by dissolving them in cell culture medium. The inoculation density should be set at 1×10^6 cells/mL, and a 96-well plate should be used for cultivation. Based on the similarities between EECs and tumor cells, and consistent with previous studies, an 18-hour culture period was employed.[10,11] In this study, 12Z cells were treated with varying concentrations of Tellimagrandin II and incubated for 18 hours to assess pro-apoptotic effects. After this period, add 10% of the culture volume of CCK-8 solution and allow incubate for another 18 hours. To determine the drug concentration that ensures a 50% cell survival rate, measure the absorbance at 450 nm. Additionally, to evaluate the time-dependent inhibitory effect of Tellimagrandin II on EECs, six time points will be established: 0 hours, 12 hours, 18 hours, 24 hours, 30 hours, and 36 hours.

Transcriptome Sequencing

A blank control group was established, and EECs were treated with Tellimagrandin II at the ideal concentration. Following 18 hours of culture, the cells were digested with trypsin, culture medium was added to stop the digestion, and the cells were then centrifuged for 5 minutes at 800 rpm. Three samples make up each group, and it is assured that each sample has a minimum of 7.5×10^6 cells. The TRIzol reagent approach was used to extract the total RNA of EECs,

and the polyA enrichment strategy was used to separate the mRNA. Reverse transcriptase was utilized to convert RNA into cDNA, which was then utilized to build the sequencing library. The Illumina high-throughput sequencing platform (Illumina HiSeq Xten/NovaSeq6000) was used to sequence the cDNA library. Align high-quality reads with the reference transcriptome and exclude low-quality reads and adapter sequences. To conduct quality control on the sequencing data, use Sickle (https://github.com/najoshi/sickle) and SeqPrep (https://github.com/jstjohn/SeqPrep). HTSeq was used to quantitatively assess the transcripts' expression level. DEGseq[12] was used for differential expression analysis. $|\log_2 FC| \geq 1$ and $P \leq 0.05$ were the criteria used to test for differentially expressed genes (DEGs).

Bioinformatics Analysis

Two sets of volcano plots were created to illustrate DEGs using the R programming language. Highlight the significant pathways of DEGs using the Kyoto Encyclopedia of Genes and Genomes(KEGG) database and represent these pathways with bubble charts. To identify highly significant pathways, perform gene set enrichment analysis (GSEA) on all gene transcripts. Present the results in a bidirectional bar chart. The intersections of the GSEA and KEGG pathways can be visualized using Venny, and the trends in these intersections can be depicted with a trend chart.

Western Blotting

Bioinformatics data is used to identify critical pathways and targets. Cells were cultivated using four different of culture media: high-dose Tellimagrandin II, Medium-dose Tellimagrandin II, low-dose Tellimagrandin II, and a blank control group. The cultivation time was consistent with the time for transcriptome sequencing. For each group, cells were harvested, RIPA protein lysis buffer added, total protein extracted, and BCA protein quantified. Denaturation, electrophoresis, membrane transfer, and blocking were then performed. After adding the corresponding dilutions of SMOX, ALDH7A1, NLRP3, β-catenin, MMP2, TIMP-1, Caspase-3, BAX, and Caspase-1 primary antibodies, the mixture was incubated for the entire night at 4°C. After adding the HRP-labeled secondary antibody, with gentle shaking at room temperature. To determine the relative expression levels of each protein after color development, utilize ImageJ for exposure and gray value computation. The detection method is the same as that of CCK-8.

Apoptosis Flow Cytometry

The cells to be evaluated were collected and washed with PBS after the four cell groups had been cultured for 6 and 18 hours. Subsequently, the cells were resuspended in Binding Buffer to adjust the cell concentration to 1×10^6 cells/mL. Then, 5 μL of Annexin V-FITC and PI were added to 100 μL of the cell suspension. The mixture was thoroughly mixed and incubated at room temperature in the dark for 15 minutes. The sample tube system is 500 μL, and the Binding Buffer is added once more once the reaction is finished. Within an hour of the dyeing being finished, the flow cytometry on-machine detection should be finished.

Transwell

To test for cell invasion, thaw the matrix gel overnight at 4°C and dilute it with serum-free medium at a ratio of 1:8 on ice. To create a substrate water film, use 24 empty plates and fill each well with 200 μL of the diluted matrix gel. After 24 hours of starvation, EECs were seeded at a cell density of 2.5×10^5 cells/mL per well. The lower chamber of the transwell plate was filled with 500 μL of 10% FBS medium, while the upper chamber contained 100 μL of high-dose Tellimagrandin II medium, 100 μL of medium-dose Tellimagrandin II medium, 100 μL of low-dose Tellimagrandin II medium, and 100 μL of serum-free medium. Following 18 hours of incubation, the cells were fixed with paraformaldehyde and stained with crystal violet. The remaining procedures were identical to those of the cell invasion assay, except that matrix gel was not required for the cell migration test.

Molecular Docking

The PDB database provided the important protein structures, while PubChem provided the 2D molecular structure of tellimagrandin II. The energy of tellimagrandin II was minimized using Chem3D, and the protein molecules' ligands and

water molecules were removed using PyMOL. After employing AutoDock to add hydrogens to the protein molecules, tellimagrandin II was used for docking. The molecular docking results were visualized with Discovery Studio 2021.

Statistical Methods

Use GraphPad Prism 9 for data analysis and graphing. For comparisons between groups, the homogeneity of variance was tested using one-way analysis of variance. When the variance was not homogeneous, the Kruskal–Wallis *H*-test employed.

Results

Optimal Concentration of Tellimagrandin II

EECs were cultivated with varying concentrations of tellimagrandin II. It was discovered that the pro-apoptotic effect of tellimagrandin II on EECs gradually increased with concentration. When EECs were exposed to 50 μg/mL of tellimagrandin II, their survival rate was guaranteed to be at least 50%. As time passed, the impact of 50 μg/mL on promoting EEC apoptosis became stronger until the inhibitory effect of tellimagrandin II on EECs approached stability at 30 and 36 hours. Please see Figure 1 for more details.

Transcriptomic Analysis of the Action of Tellimagrandin II on EECs

Tellimagrandin II was chosen to act on EECs at a concentration of 50 μg/mL based on the outcomes of the CCK-8 experiment. Eighteen hours after culturing the EECs, sequencing was carried out. The two cell groups had 1688 DEGs in total, of which 798 were down-regulated and 890 were up-regulated. Please see Figure 2a for more information. The sequencing data can be found in Supplementary File 1. Using KEGG analysis, 34 significant (P ≤0.05) pathways were enhanced. This comprises cell adhesion-related TGF-β and ECM-receptor interaction signaling pathways, as well as cell proliferation-related PI3K-Akt and Wnt signaling pathways. TNF and IL-17 signaling pathways are linked to inflammation, while beta-alanine metabolism and mTOR signaling pathways are linked to metabolism. The beta-alanine metabolism pathway has the lowest p-value among them. Please see Figure 2b for more information. 59 highly significant pathways (Padjust ≤0.05) were found using GSEA enrichment analysis, of which 50 were activated and 9 were inhibited. Please see Figure 3a for more information. The intersection of the pathways identified from KEGG and GSEA gives 13 pathways. For more information, see Figure 3b. Use trend charts to highlight four endometriosis-related pathways, including apoptosis, ECM-receptor interaction, and the IL-17 signaling pathway, as well as the most prominent beta-Alanine metabolism in the KEGG pathway. For more information, please see Figure 3c–f.

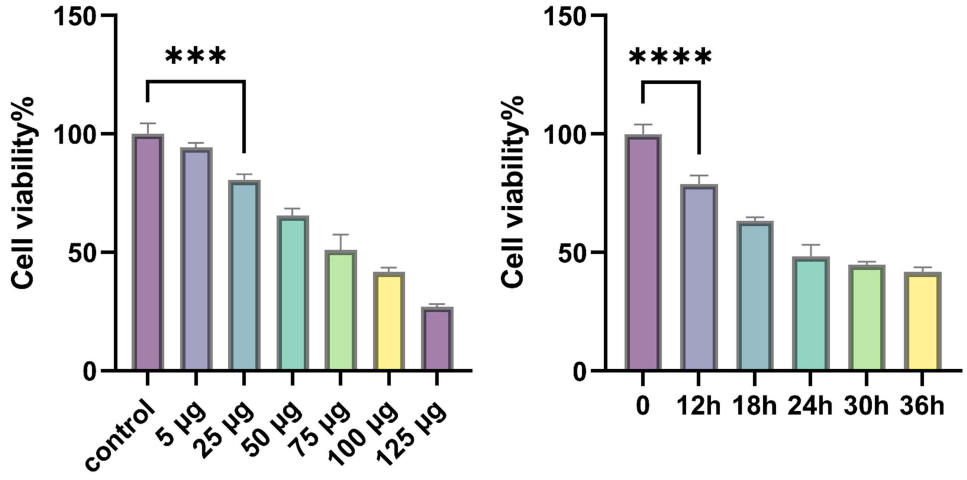

Figure 1 CCK-8 assay. (**Left**) The effect of varying concentrations of tellimagrandin II on the survival rate of EECs; (**Right**) The effect of 50 μg/mL tellimagrandin II on the survival rate of EECs at different time points. ***:P <0.001; ****P <0.0001.

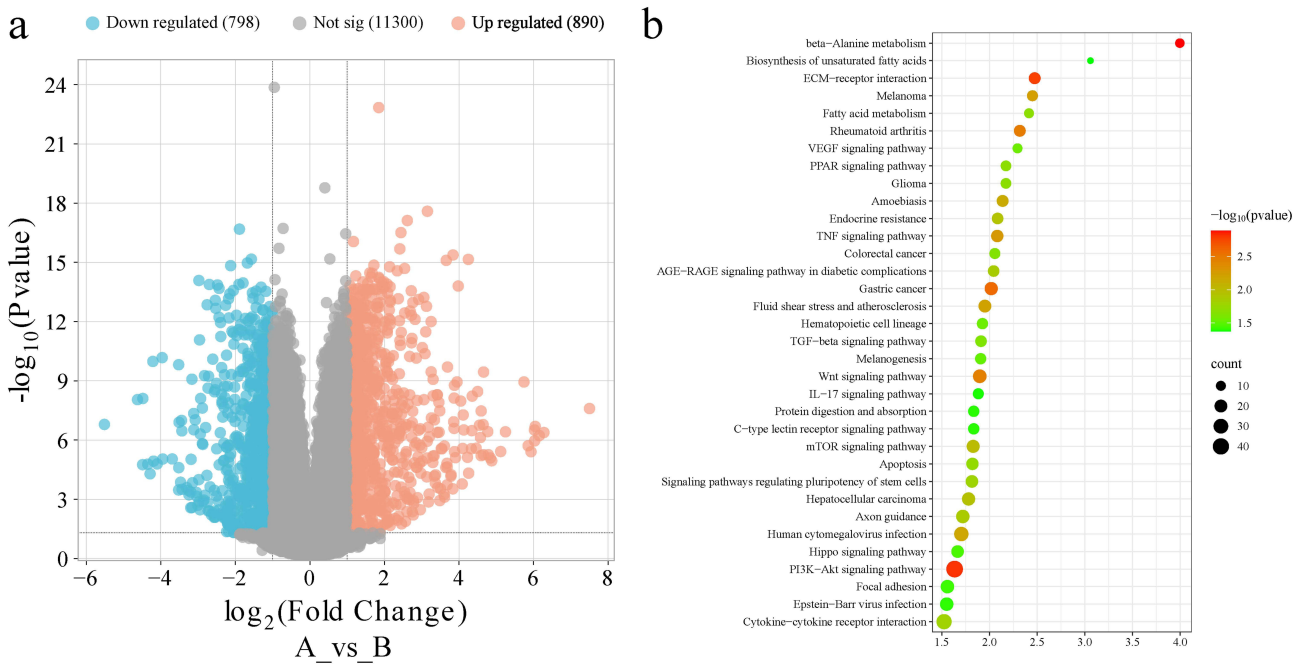

Figure 2 The figure shows the basic analysis of Tellimagrandin II acting on EECs: (**a**) depicts the expression details of all DEGs, with Orange dots indicating upregulation and blue dots indicating downregulation; (**b**) represents the KEGG enrichment analysis. The hue of the bubbles signifies the P-value, while their size represents the number of enriched DEGs. The redder the color, the more statistically significant the enrichment pathway.

Tellimagrandin II Promotes the Accumulation of 3-Aminopropanal in EECs and Thereby Activates Inflammasomes

Tellimagrandin II intervention causes EECs to undergo apoptosis and activates the IL-17 signaling pathway, as seen in Figures 3d and f. This suggests that Tellimagrandin II can encourage EECs' apoptosis and their own inflammatory response. Few prior studies have examined how elements of traditional Chinese medicine can promote inflammation. In addition to the IL-17 pathway, other inflammatory pathways like NFκB, TNF, and JAK-STAT have also been triggered. This suggests that Tellimagrandin II may cause EECs to undergo apoptosis via inflammation. Furthermore, Tellimagrandin II prevents EECs from metabolizing beta-alanine. Given the antioxidant properties of beta-alanine,[13] we hypothesize that the blockage of the beta-alanine metabolic pathway may be linked to EECs apoptosis and inflammation. The high, medium and low doses of Tellimagrandin II are 50 μg/mL, 40 μg/mL and 25 μg/mL respectively. Tellimagrandin II was shown to suppress ALDH7A1 expression and boost SMOX expression using WB detection; this effect strengthening when the dosage was increased. Figures 4a–c provide more information. This causes 3-aminopropanal to accumulate in the intracellular membrane by increasing the conversion of Spermine to 3-aminopropanal and decreasing the conversion of 3-aminopropanal to beta-Alanine. 3-aminopropanal has the ability to activate inflammasomes after accumulation.[14,15] Additionally, it was shown that Tellimagrandin II might encourage the upregulation of the inflammatory proteins Caspase-1 and NLRP3. Figures 4a, d, and e provide more information.

Tellimagrandin II May Promote EEC Apoptosis via Inflammasome Activation While Inhibiting EEC Invasion and Migration

Independent of gasdermin, inflammasomes can increase the expression of BAX and Caspase-3,[16,17] which in turn promotes apoptosis. Tellimagrandin II has the ability to increase BAX and Caspase-3 expression, and this effect is positively correlated with the dosage. This indicates that Tellimagrandin II may promote EECs apoptosis by activating the inflammasome. Please see Figures 4a, g, and h for more information. Moreover, inflammasomes have the ability to suppress β-catenin expression, which can increase MMP2 production and enhance cell invasiveness. Western blotting

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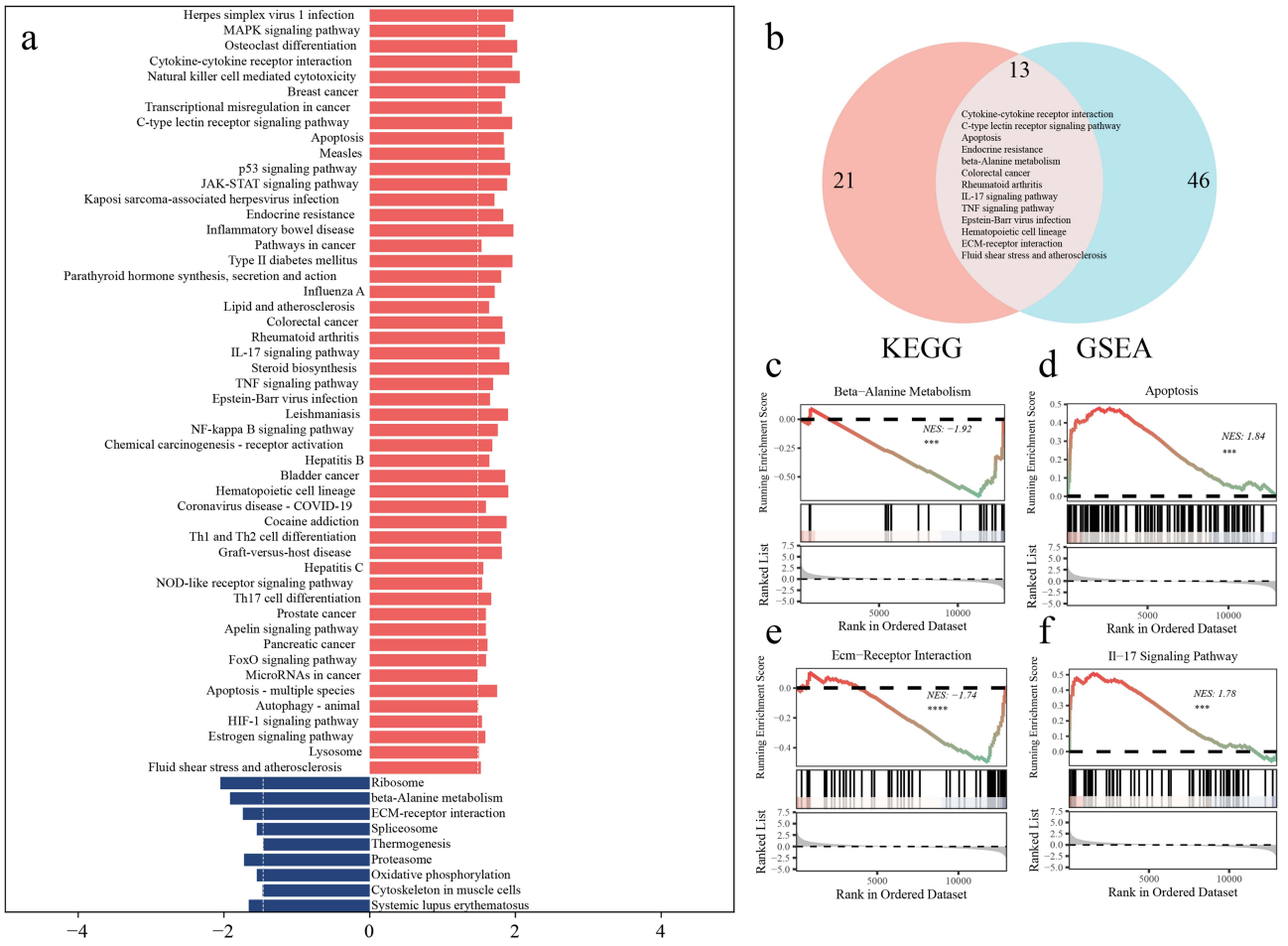

Figure 3 Shows the GSEA enrichment analysis: (**a**) depicts the alterations in the pathway following Tellimagrandin II action on EECs, with red bars indicating activation and blue bars indicating inhibition; (**b**) depicts the 13 pathways where KEGG intersects with GSEA; (**c**) represents beta-alanine metabolism; (**d**) represents apoptosis; (**e**) represents ECM-receptor interaction; and (**f**) represents the IL-17 signaling pathway. On the c-f curves, an upward protrusion suggests activation, whereas a downward protrusion implies inhibition. ***:P <0.001; ****P <0.0001.

revealed that Tellimagrandin II may increase the expression of TIMP1 while downregulating that of MMP2 and β-catenin. Please see Figures 4a, f, i, and j for more information.

Transwell detected the invasion and migration of the four cell groups, while flow cytometry detected the apoptosis of the four cell groups. It was found that Tellimagrandin II might limit EECs' invasion and migration while also encouraging EECs' apoptosis. Furthermore, the effects of high-dose Tellimagrandin II were more pronounced. Among these, the cells' late apoptosis was evident when Tellimagrandin II intervened in EECs for eighteen hours. Refer to Figures 5 and 6 for more information.

Tellimagrandin II Can Bind Effectively to SMOX and ALDH7 Molecules

The mechanism of Tellimagrandin II on EECs was demonstrated using a diagram. Tellimagrandin II, as illustrated in Figure 7, can accumulate 3-aminopropanal by inhibiting the expression of ALDH7 and promoting the expression of SMOX. The accumulation of 3-aminopropanal activates the NLRP3 and Caspase-1 inflammasomes. Increased NLRP3 levels reduce β-catenin expression, thereby decreasing MMP2 levels. Caspase-1 induces the expression of Caspase-3 and BAX, which promote cell death. Tellimagrandin II's binding sites to SMOX and ALDH7 were demonstrated via molecular docking and exhibited in both 2D and 3D visuals. Tellimagrandin II has a minimum energy of −8.9kcal/mol for binding to SMOX and −10.7kcal/mol for binding to ALDH7. For further details, please refer to Figure 8.

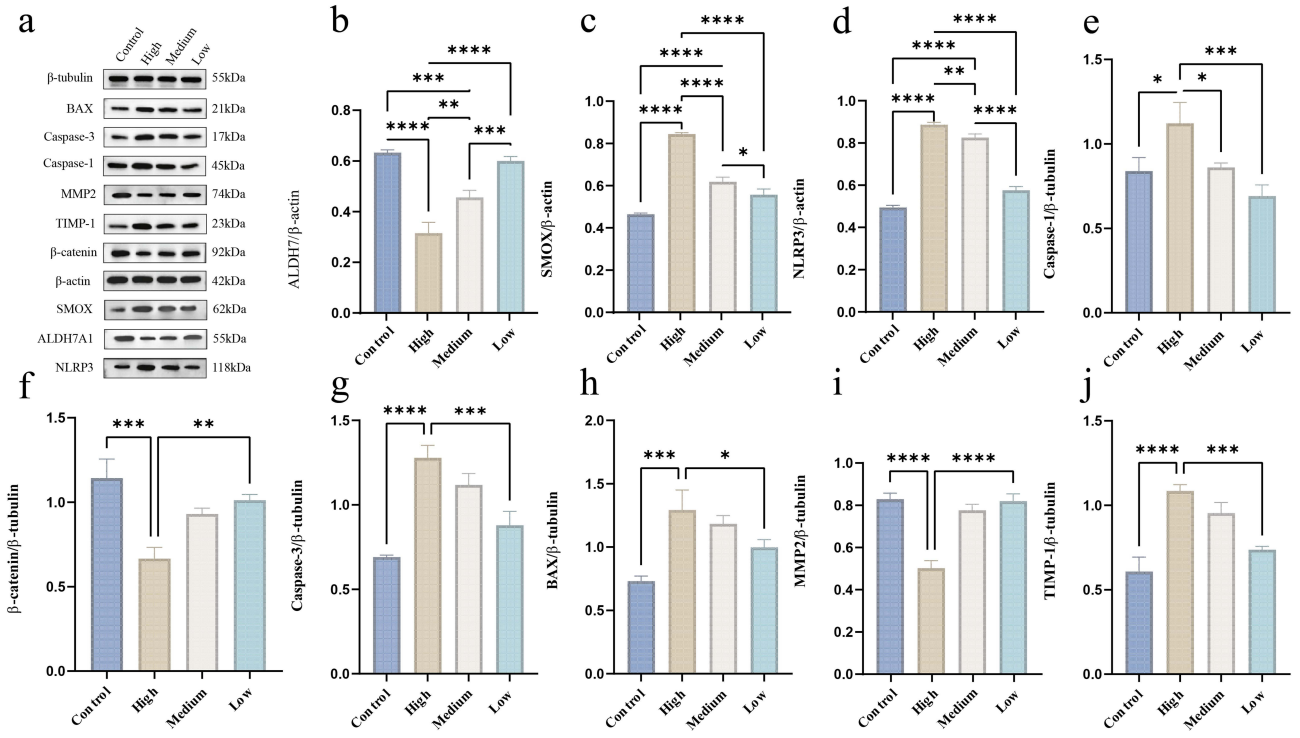

Figure 4 Western blot analysis of EECs treated with Tellimagrandin II: (**a**) protein immunoblot; (**b**) ALDH7A1; (**c**) SMOX; (**d**) NLRP3; (**e**) Caspase-1; (**f**) β-catenin; (**g**) cleaved Caspase-3; (**h**) BAX; (**i**) MMP2; (**j**) TIMP1. Each experiment was repeated three times. *:P <0.05; **:P <0.01; ***:P <0.001; ****P <0.0001.

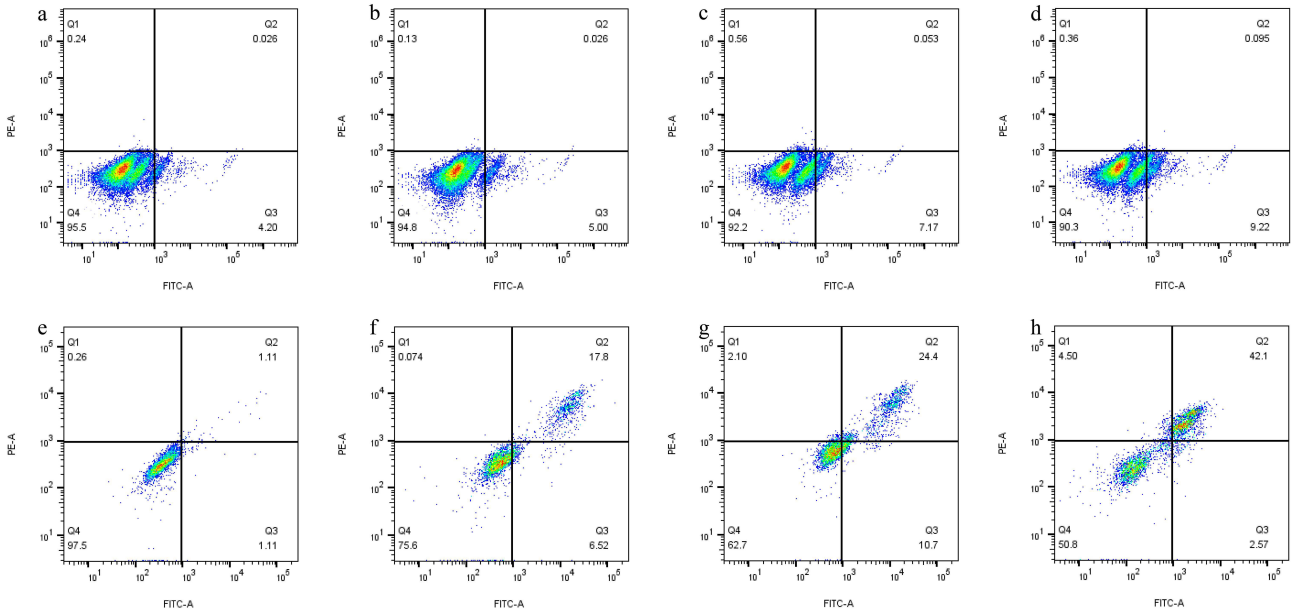

Figure 5 Apoptosis flow cytometry analysis. (**a**–**d**) show flow cytometry results of EECs treated with Tellimagrandin II for 6 hours, while (**e**–**h**) show results after 18 hours of treatment. (**a** and **e**) represent the control group; (**b** and **f**) represent the low-dose Tellimagrandin II group; (**c** and **g**) represent the medium-dose group; (**d** and **h**) represent the high-dose group. The vertical axis represents PI (propidium iodide) staining, and the horizontal axis represents Annexin V staining.

Discussion

EECs resemble tumors and can avoid immune cell surveillance, allowing them to proliferate indefinitely.[18,19] Numerous studies have demonstrated that in the early stages of endometriosis, lesions predominantly exist in a pro-inflammatory environment, allowing more immune killer cells to focus on eliminating EECs.[20,21] However, in the latter stages of

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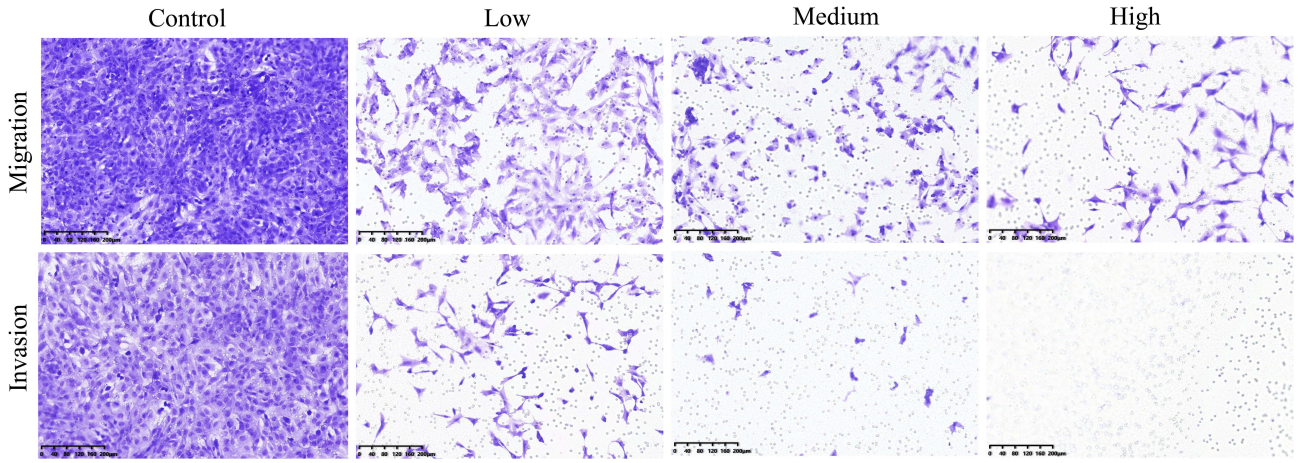

Figure 6 Cell invasion and migration experiments. High, medium, and low doses of Tellimagrandin II can all inhibit the invasion and migration of EECs.

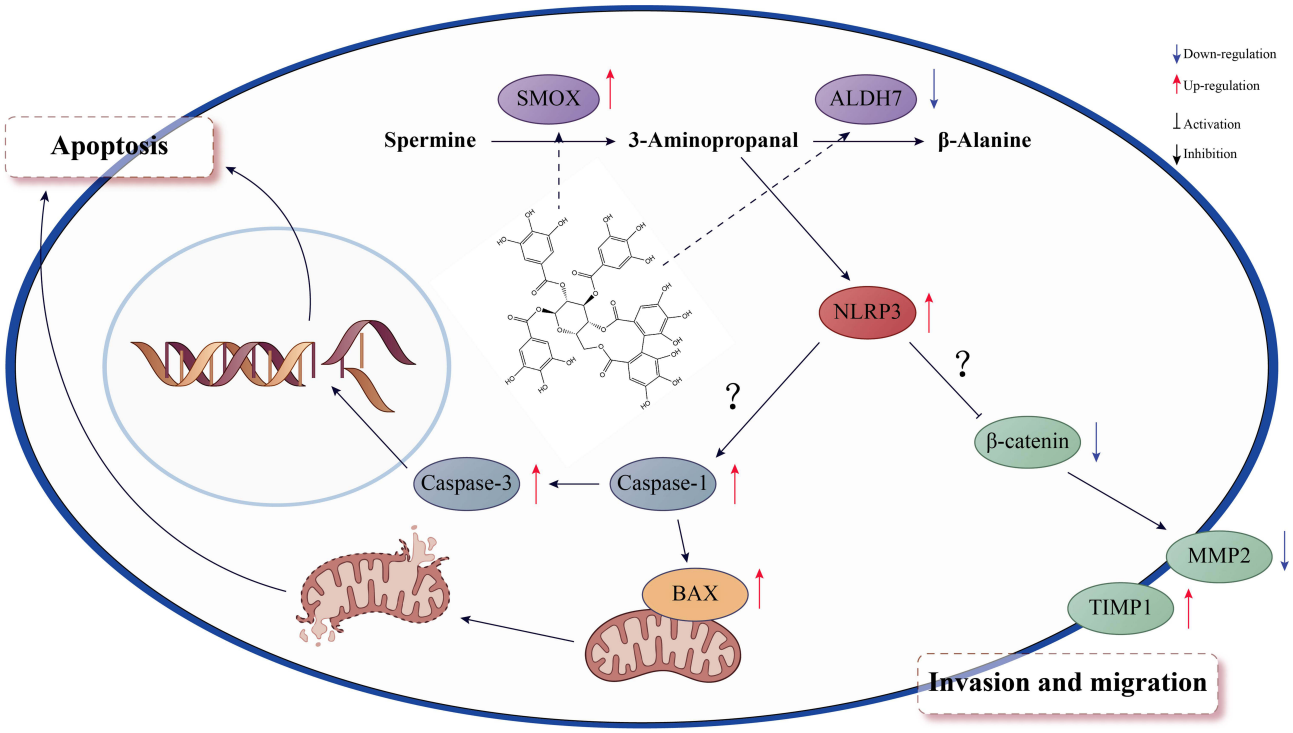

Figure 7 Molecular mechanism of Tellimagrandin II in the treatment of endometriosis. Tellimagrandin II (TII) may increase SMOX expression and decrease ALDH7 expression, leading to the accumulation of 3-aminopropanal in endometrial epithelial cells (EECs). The accumulated 3-aminopropanal can activate the inflammasome. Upon inflammasome activation, it may promote MMP2 expression via β-catenin and induce apoptosis by activating Caspase-1. However, whether TII inhibits invasion and promotes apoptosis in EECs through the inflammasome pathway requires further experimental verification.

endometriosis, the lesions are primarily anti-inflammatory, and the immune cells are predominantly anti-inflammatory, allowing the EECs to develop freely.[22,23] In contrast to the anti-inflammatory effects of earlier active ingredients in herbal, the findings of this study suggest that Tellimagrandin II may encourage inflammation in EECs, which in turn promotes the cells' apoptosis and impairs their capacity for invasion and migration. The accumulation of 3-Aminopropanal may be connected to the development of this inflammation. Spermine can be converted to 3-Aminopropanal by SMOX, while 3-Aminopropanal can be converted to beta-Alanine by ALDH7. Tellimagrandin II can cause 3-Aminopropanal to accumulate via up-regulating SMOX and down-regulating ALDH7.[24,25] Perhaps Tellimagrandin II can also regulate the activity of related enzymes, thereby allowing 3-Aminopropanal to accumulate. This also requires further research to confirm.

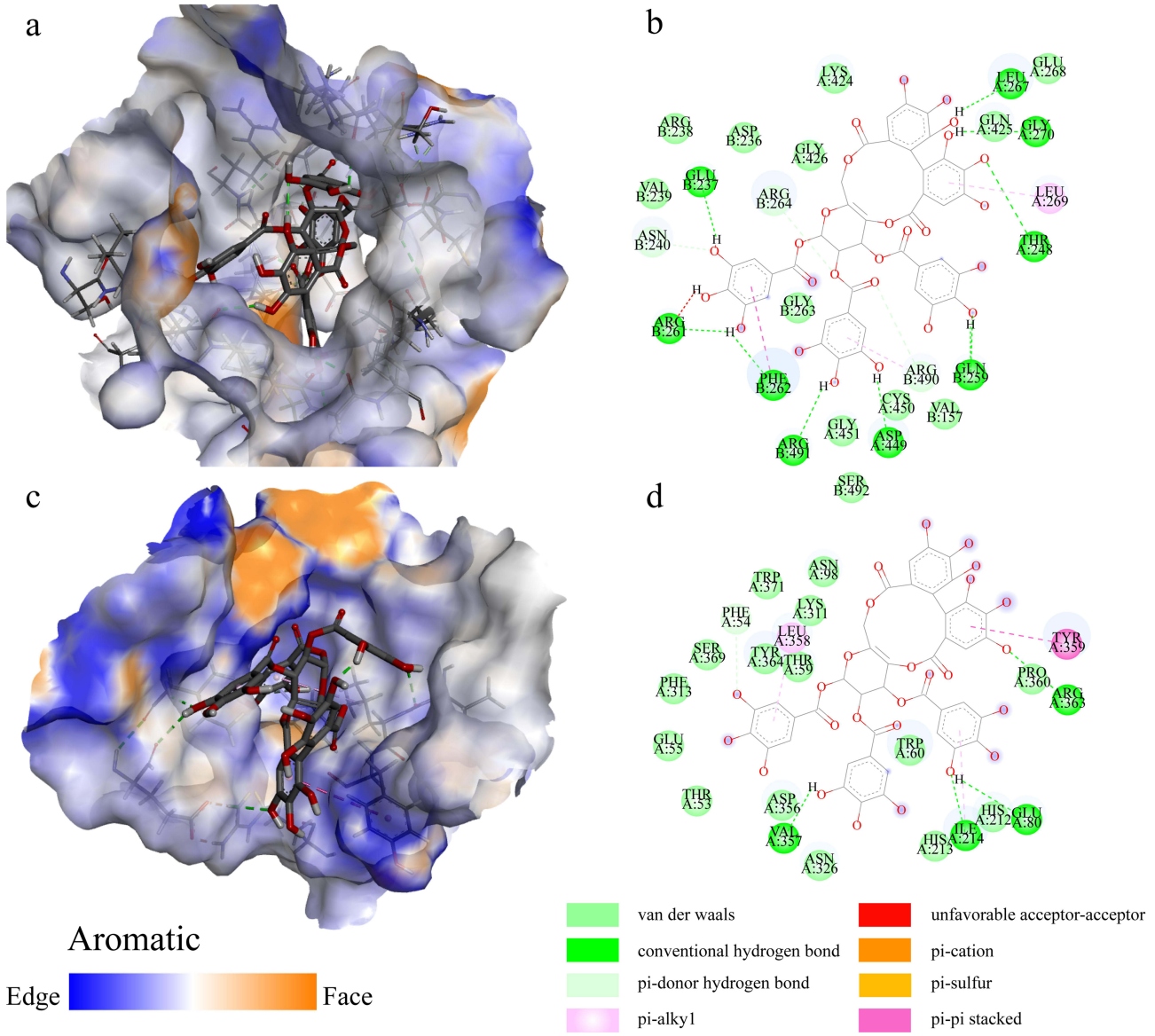

Figure 8 Molecular docking diagram: (**a**) 3D representation of the docking between ALDH7A1 and Tellimagrandin II; (**b**) 2D representation of the docking between ALDH7A1 and Tellimagrandin II; (**c**) 3D representation of the docking between SMOX and Tellimagrandin II; (**d**) 2D representation of the docking between SMOX and Tellimagrandin II.

3-aminopropanal is a cytotoxin that can cause lysosomes to burst and encourage oxidative stress and cell death.[26,27] Cellular oxidative stress can trigger the activation of inflammasomes.[28] Additionally, our findings demonstrated that Tellimagrandin II may promote 3-aminopropanal accumulation and increase the expression of the intracellular inflammasome marker NLRP3. The expression of Caspase-1 can be activated by NLRP3, and Caspase-1 can activate BAX and Caspase-3.[29,30] The mitochondrial membrane can be destroyed by BAX, and nuclear DNA can be harmed by caspase-3. Both may induce cell apoptosis.[31,32] Endometriosis is a chronic inflammatory illness, and ectopic lesions activate inflammasomes.[33] Cell apoptosis can result from Tellimagrandin II's promotion of EECs' inflammasome activation. This suggests that Tellimagrandin II may cause excessive inflammation in cells, which in turn may induce cell death. Tellimagrandin II may also activate inflammatory pathways, such as JAK-STAT, NF-κB, and IL-17, in EECs, as indicated by GSEA enrichment analysis. We need to investigate whether increased inflammation of EECs will lead to an increase in the body's immune cells attacking them.

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MMP2 can degrade the extracellular matrix, which permits the invasion of endometriotic cells. Endometriosis lesions exhibit increased MMP2 expression and decreased TIMP-1 expression, which can inhibit MMP2.[34,35] Additionally, MMP2 expression is increased in endometriosis lesions and can be promoted by β-catenin.[36,37] The presence of inflammation typically suppresses β-catenin activity, and β-catenin suppresses inflammation,[38–40] β-catenin expression is suppressed following NLRP3 activation. Gong et al[41] conducted research showing that the Yangzheng mixture can inhibit the migration of liver cancer cells through the NF-κB/NLRP3/β-catenin pathway. In liver cancer cells, the expression of NLRP3 increases while the expression of β-catenin decreases, resulting in a reduced cell migration ability. This also indicates the correlation between NLRP3 and β-catenin. Our findings suggest that β-catenin and MMP2 expression decline following NLRP3 activation. However, whether NLRP3 activation directly downregulates β-catenin and MMP-2 expression remains to be verified.

Conclusion

This study provides preliminary evidence of the in vitro mechanism of action of Tellimagrandin II in endometriosis. It may lead to the accumulation of 3-aminopropanal in EECs, which can activate inflammasomes. It inhibits cell invasion and migration and induces cell death once inflammasomes are activated. Given that inflammasomes are constitutively active in endometriosis, the inhibitory effect of Tellimagrandin II via inflammasome activation still requires further verification. By inducing inflammatory responses, Tellimagrandin II may render EECs more susceptible to immune surveillance, thereby enhancing their clearance by immune cells. Nevertheless, additional in vivo research is needed to validate this. In addition, this study has not yet interfered on normal human cells to determine whether Tellimagrandin II has any detrimental effects on various types of normal human cells. What is worth examining in the future is that we will next examine the influence of Tellimagrandin II on the activities of SMOX and ALDH7A1.

Abbreviations

EECs, Ectopic endometrial cell; SMOX, Spermine Oxidase; ALDH7A1, Aldehyde Dehydrogenase 7A1; NLRP3, NLR Family, Pyrin Domain Containing Protein 3; β-Catenin, beta Catenin; MMP2, Matrix Metallopeptidase 2; TIMP1, Tissue Inhibitors of Metalloproteinase 1; Bax, Bcl-2-associated X; GSEA, gene set enrichment analysis; DEGs, differentially expressed genes; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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