UNIVERSA MEDICINA

pISSN: 1907-3062 / eISSN: 2407-2230

Univ Med 2026;45:199-206

DOI: https://doi.org/10.18051/UnivMed.2026.v45.199-206

# ORIGINAL ARTICLE

# Dendrophthoe pentandra (*Mango Mistletoe*) leaves modulate steroidogenic acute regulatory protein, aromatase, and estrogen receptor expression in aged mice

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Date of first submission, January 12, 2026
Date of final revised submission, June 23, 2026
Date of acceptance, July 7, 2026

Cite this article as: Indahwati L, Wati LR, Sermoati IA, Handono K, Riawan W. Dendrophthoe pentandra (*Mango Mistletoe*) leaves modulate steroidogenic acute regulatory protein, aromatase, and estrogen receptor expression in aged mice. Univ Med 2026;45:199-206

## ABSTRACT

**BACKGROUND**

Ovarian aging is associated with impaired steroidogenesis and estrogen signaling, contributing to reproductive dysfunction. *Dendrophthoe pentandra* (Mango Mistletoe), a flavonoid-rich plant with antioxidant properties, has demonstrated anti-inflammatory and cytoprotective effects in experimental studies. However, its role in modulating the integration of ovarian steroidogenic and estrogen-responsive pathways during aging remains unclear. This study evaluated the effects of *D. pentandra* leaf extract on the expression of steroidogenic acute regulatory protein (StAR), aromatase (CYP19A1), estrogen receptor α (ERα), and ERβ in aged female mice.

**METHODS**

This experimental study included 25 female mice: 5 young (8–12 weeks) and 20 aged (18–20 months). Animals were allocated to five groups (n=5 per group): young controls, aged controls, and three aged treatment groups receiving *D. pentandra* leaf extract at doses of 150, 300, and 600 mg/kg BW, respectively, for 30 days. Protein expression was evaluated using immunohistochemistry and analyzed using one-way ANOVA followed by Tukey HSD post hoc test.

**RESULTS**

Aged mice exhibited significantly lower expression of StAR, aromatase, ERα, and ERβ compared with young controls. Administration of *D. pentandra* extract significantly increased expression of all evaluated markers in a dose-dependent manner ($p<0.001$). Post hoc analysis demonstrated significant restoration of steroidogenic and estrogen-signaling–related protein expression, particularly in the highest-dose group, where aromatase, ERα, and ERβ expression approached or exceeded levels observed in young controls.

**CONCLUSION**

*D. pentandra* leaf extract restored key components of ovarian steroidogenesis and estrogen signaling in aged mice, suggesting potential phytoendocrine modulatory activity against age-related ovarian endocrine decline.

**Keywords:** *Dendrophthoe pentandra,* STAR, aromatase, estrogen receptors, reproductive aging, mice

## INTRODUCTION

Reproductive aging is a natural yet complex biological process characterized by a progressive decline in ovarian functional capacity, accompanied by a gradual reduction in fertility and endocrine output.[1] This transition reflects a loss of ovarian reserve and dysregulated hormone secretion, which has profound implications for reproductive and overall health in females.[2] Ovarian aging is marked by a progressive decline in oocyte competence, a reduction in the follicular reserve, and disturbances in hormonal regulation, leading to reduced sex hormone secretion and systemic effects that extend beyond fertility decline.[3] This transition has been closely associated with decreased activity of key proteins involved in steroidogenesis and estrogen signaling, including the steroidogenic acute regulatory protein (StAR), the aromatase enzyme (CYP19A1), and the estrogen receptors ERα and ERβ, which collectively regulate sex hormone synthesis and action.[2,4] Steroidogenic acute regulatory protein mediates the rate-limiting step of mitochondrial cholesterol transport, which is essential for steroid biosynthesis.[5] Aromatase catalyzes the conversion of androgens to estrogens, and ERα/ERβ transmit estrogenic signals that influence reproductive functions and systemic homeostasis.[4,6]

These molecular components play a central role in maintaining reproductive homeostasis. Their age-related downregulation not only compromises fertility but also contributes to systemic consequences of estrogen deficiency, such as vasomotor symptoms, mood disturbances, osteoporosis, and cardiovascular changes frequently observed in post-reproductive females.[7] Although hormone replacement therapy (HRT) is widely used to manage these symptoms, concerns regarding its long-term risks, including cardiovascular complications and hormone-dependent malignancies, have driven increasing interest in safer and more natural alternatives.[8]

In response to this need, plant-derived compounds with estrogenic or hormone-modulating properties have attracted increasing attention as potential supportive approaches for reproductive aging. Phytoestrogens and plant polyphenols have been proposed as natural alternatives to conventional hormone replacement therapy, owing to their ability to interact with estrogen receptors and modulate estrogen signaling pathways.[8] However, despite growing interest, scientifically validated herbal interventions for age-related reproductive decline remain limited. Most existing research has focused on well-known phytoestrogen sources such as soy isoflavones and flaxseed lignans, while indigenous botanicals with comparable potential remain largely unexplored. One such plant is Dendrophthoe pentandra (mango mistletoe), a hemiparasitic species traditionally used in Southeast Asian medicine and reported to possess various pharmacological activities, including antioxidant,[9] anti-inflammatory,[10] antiproliferative,[11] immunomodulatory, and anti-aging effects.[12] Experimental studies have shown that the extract enhances T-cell activation and cytokine production, reduces inflammatory markers, and regulates cell proliferation and apoptosis through pathways involving p53, p21, and survivin.[11,13,14] However, existing studies have largely focused on immune, inflammatory, metabolic, and cancer-related conditions, whereas its potential role in reproductive aging and ovarian function remains largely unexplored. In particular, the effects of D. pentandra on ovarian steroidogenesis and estrogen biosynthesis pathways involving StAR and aromatase have not been investigated. Although some mistletoe species contain bioactive compounds that may influence hormone production, direct evidence regarding the modulation of these steroidogenic enzymes requires targeted in vivo and in vitro studies.

Therefore, the present study aimed to investigate whether the *D. pentandra* leaf extract could influence the expression of StAR, aromatase, ERα, and ERβ in the ovaries of aged female mice. These proteins are key regulators of steroidogenesis and estrogen signaling and may serve as molecular indicators of age-related endocrine decline.

## METHODS

### Research design

This study employed a laboratory experimental design with an aging mouse model to evaluate the effects of *Dendrophthoe pentandra* (mango mistletoe) leaf extract on the expression of steroidogenic and estrogen-signaling-related proteins. The study was conducted at the Laboratory of Experimental Animal

Development, Faculty of Medicine, Universitas Brawijaya, Indonesia, from September to November 2020.

**Study subjects**

Eight-to-twelve-weeks-old young female BALB/c mice and 18-to-20-months-old aged female BALB/c mice, weighing 30–35 g, were used in this study. The young mice served as subjects with normal steroidogenic capacity, while the aged mice served as a model of age-related decline in steroidogenesis. All animals were housed in standard laboratory cages at the Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia. Animals were maintained under controlled conditions at 26–27 °C and had free access to standard laboratory chow and drinking water. A 7-day acclimatization period was provided prior to the experiment. Mice that became sick, pregnant, or died during the study period were excluded from the analysis

**Sample size determination**

A total of 25 female mice were included in this study, consisting of five 8 to 12-weeks-old young mice and 20 18 to 20-months-old aged mice.[15]Animals were divided into five experimental groups, with five mice allocated to each group, comprising one young control group (n=5), one aged control group, and three aged treatment groups receiving *D. pentandra* leaf extract at doses of 150, 300, and 600 mg/kg body weight, respectively.

**Preparation of *Dendrophthoe pentandra* leaf extract**

*D. pentandra* leaves were obtained in simplicia form from UPT Materia Medica, Batu, Indonesia. The dried leaves were macerated using 96% ethanol for 72 hours. The macerate was filtered, and the filtrate was evaporated under reduced pressure to obtain a concentrated paste-like extract.

**Administration of *Dendrophthoe pentandra* leaf extract**

The extract was appropriately diluted and administered orally using a feeding cannula at a volume of 0.5 mL per dose. The aged mice in the three treatment groups received *D. pentandra* leaf extract at doses of 150, 300, and 600 mg/kg body weight, respectively. The extract was administered once daily for 30 consecutive days by trained laboratory personnel from the Faculty of Medicine, Universitas Brawijaya.

**Measurements**

Expression of StAR, aromatase, ERα, and ERβ was assessed using immunohistochemistry (IHC). Ovarian tissues were processed according to standard IHC procedures. Semi-quantitative evaluation of protein expression was performed using the Remmele immunoreactive score (IRS), expressed in IRS units ranging from 0 to 12. Each ovarian tissue sample was analyzed in duplicate to ensure measurement reliability. The duplicate measurements represented technical replicates and were averaged for statistical analysis.

**Statistical analysis**

Data distribution and homogeneity of variance were assessed using the Shapiro–Wilk and Levene's tests prior to statistical analysis. Data were evaluated using one-way analysis of variance (ANOVA) to assess differences between groups. When significant differences were identified, Tukey's honest significant difference (HSD) post hoc test was used for multiple comparisons, with $p<0.05$ considered statistically significant.

**Ethical clearance**

This study was approved by the Ethics Committee of Universitas Brawijaya (Approval No. 161/EC/KEPK/09/2020) and was performed in compliance with internationally recognized standards for the care and use of laboratory animals.

## RESULTS

The effects of *Dendrophthoe pentandra* (mango mistletoe) leaf extract on ovarian steroidogenic and estrogen signaling-related markers were evaluated in young and aged mice. Significant differences in ERα, ERβ, aromatase, and StAR expression were observed among the experimental groups (Table 1).

Aged control mice exhibited markedly lower expression of ERα, ERβ, aromatase, and StAR than did young control mice ($p<0.001$). Administration of *D. pentandra* extract progressively increased the expression of all evaluated markers in a dose-dependent manner.

**Table 1**. Effect of *Dendrophthoe pentandra* leaf extract on ERα, ERβ, aromatase, and StAR expression in ovarian tissue of young and aged mice

| | Treatment groups | | | | | p value |
|---|---|---|---|---|---|---|
| | K1 (n=5) | K2 (n=5) | P1 (n=5) | P2 (n=5) | P3 (n=5) | |
| Erα (IRS Score) | $11.5 \pm 11.62^{ab}$ | $6.4 \pm 1.19^{c}$ | $9.9 \pm 1.14^{b}$ | $11.7 \pm 1.44^{ab}$ | $13.7 \pm 1.25^{a}$ | <0.001 |
| Erβ (IRS Score) | $4.1 \pm 0.96^{b}$ | $1.7 \pm 0.84^{c}$ | $4.7 \pm 1.04^{b}$ | $5.2 \pm 0.91^{b}$ | $7.3 \pm 1.15^{a}$ | <0.001 |
| Aromatase (IRS Score) | $10.6 \pm 0.42^{a}$ | $3.1 \pm 1.08^{c}$ | $6.2 \pm 1.40^{b}$ | $9.5 \pm 1.41^{a}$ | $11.4 \pm 0.55^{a}$ | <0.001 |
| StAR (IRS Score) | $10.3 \pm 1.04^{a}$ | $4.0 \pm 0.94^{d}$ | $6.2 \pm 1.35^{c}$ | $8.2 \pm 0.57^{b}$ | $10.2 \pm 0.97^{a}$ | <0.001 |

Data are presented as mean ± SD. IRS: immunoreactive score (0–12); K1: young control group; K2: aged control group; P1: 150 mg/kgBW; P2: 300 mg/kgBW; P3: 600 mg/kgBW. Different superscript letters indicate statistically significant differences among groups ($p<0.05$)

Tukey's HSD multiple-comparison test demonstrated significant differences between the aged control group and treatment groups, particularly at doses of 300 and 600 mg/kg BW. Expression levels of aromatase and StAR in the highest-dose group approached those observed in young control mice, while ERα and ERβ expression also increased following extract administration, suggesting improved responsiveness of estrogen signaling in treated aged mice.

Figure 1 shows the progressive decline in ERα, ERβ, aromatase, and StAR expression in aged mice compared with young controls, followed by dose-dependent enhancement after *D. pentandra* administration. A dose-dependent increase in all evaluated markers was observed across treatment groups, with the strongest restorative pattern identified in the 600 mg/kg BW group. The visual distribution of data showed expression levels approaching those of young control mice, particularly for aromatase and StAR.

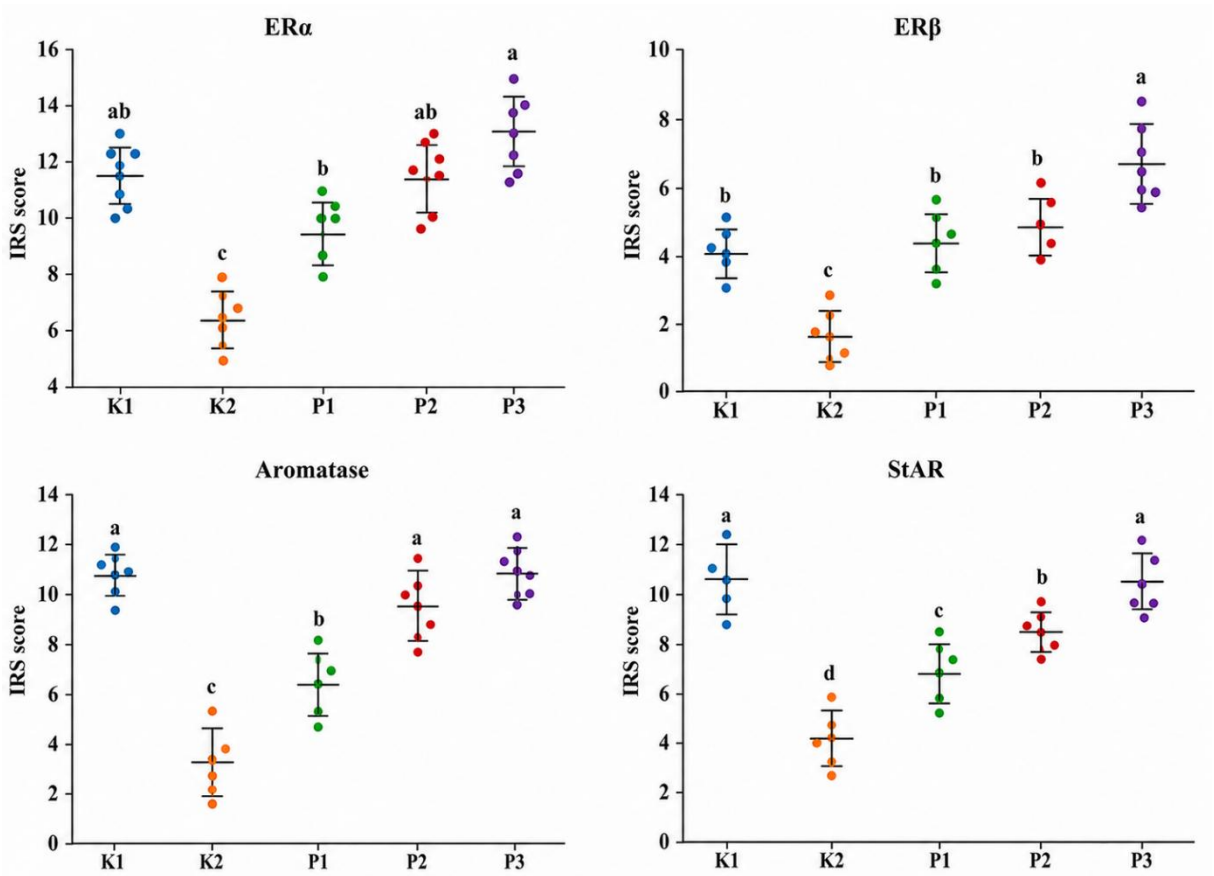


**Figure 1**. Expression of ERα, ERβ, aromatase, and StAR in ovarian tissue among experimental groups. Each dot represents one mouse (n=5/group), and error bars indicate mean ± SD. Different superscript letters indicate statistically significant differences among groups ($p<0.05$).

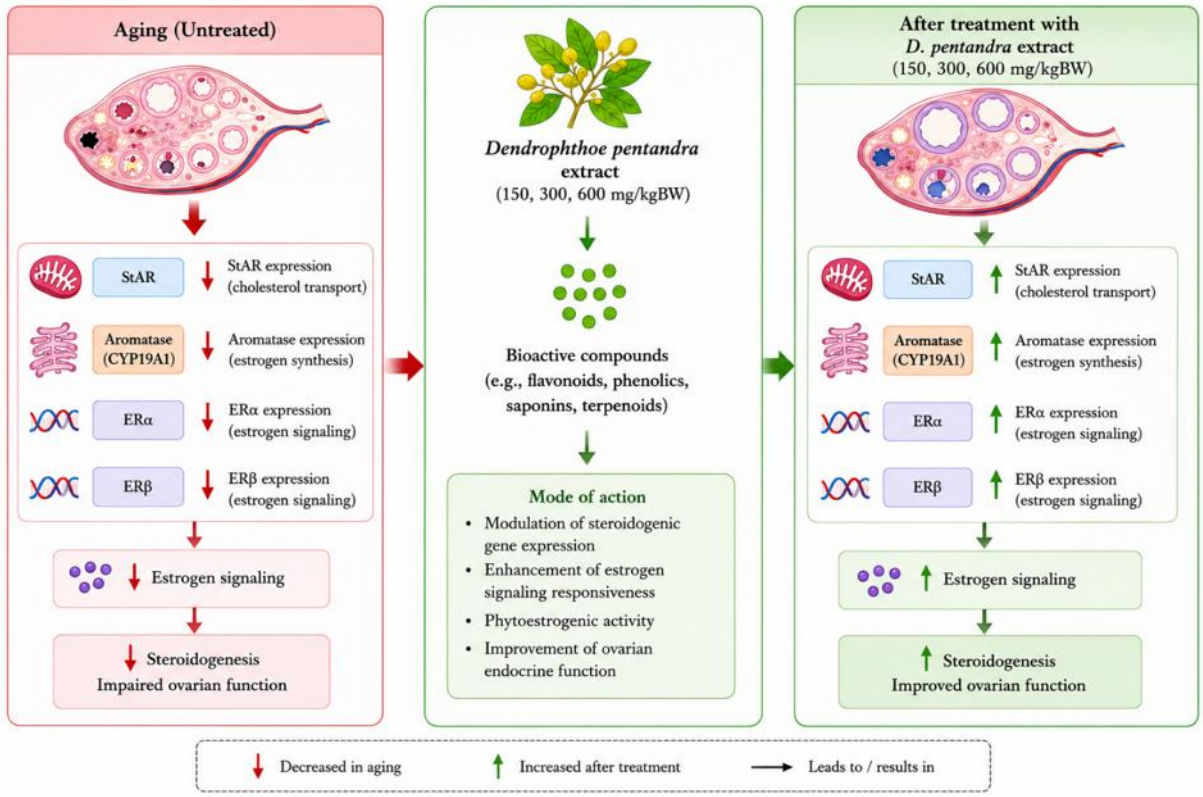


**Figure 2**. Illustrates the proposed mechanism underlying the protective effects of *D. pentandra* extract on ovarian endocrine aging. Aging was associated with decreased expression of StAR, aromatase (CYP19A1), ERα, and ERβ, thereby impairing steroidogenesis and estrogen signaling.[1,7,8,16–20] Administration of *D. pentandra* extract may improve ovarian endocrine function in aged mice by modulating steroidogenic and estrogen signaling pathways

## DISCUSSION

The present study demonstrated that ovarian aging was associated with reduced expression of StAR, aromatase, ERα, and ERβ in aged mice, indicating impaired steroidogenesis and estrogen signaling during reproductive aging. Administration of *D. pentandra* leaf extract progressively restored the expression of all evaluated markers in a dose-dependent manner, with the highest dose showing the strongest restorative effect. These findings suggest that *D. pentandra* may modulate both ovarian steroidogenic activity and estrogen receptor activity in aging ovarian tissue.

Treatment with *Dendrophthoe pentandra* (mango mistletoe) leaf extract produced a graded modulation of StAR expression in aged mice, with higher doses approaching the levels observed in young animals. This dose-dependent effect suggests that *D. pentandra* may enhance steroidogenic activity in aging ovarian tissue. Restoration of StAR expression may indicate partial recovery of early steroidogenic processes that are commonly impaired during ovarian aging, thereby supporting ovarian endocrine function during reproductive senescence.[5,8,21] Previous phytochemical studies have reported that ethanolic extracts of *D. pentandra* contain various bioactive compounds, including flavonoids, phenolics, tannins, alkaloids, terpenoids, and saponins, many of which exhibit antioxidant and hormone-modulating activities.[14,22,23] These compounds may contribute to the observed enhancement of steroidogenic markers in aging ovarian tissue by protecting against oxidative stress and maintaining cellular steroidogenic function.[21,24]

Aromatase (CYP19A1) plays a central role in estrogen biosynthesis by catalyzing the conversion of androgens into estrogens within ovarian granulosa cells. Reduced aromatase expression is considered an important molecular feature of ovarian aging and contributes to the decline in estrogen production in aging females.[2,6] Consistent with this concept, aged mice in the present study exhibited substantially reduced aromatase expression compared with

young controls, indicating impaired ovarian estrogen production.

Administration of *D. pentandra* extract increased aromatase expression in a dose-dependent manner, with the highest dose restoring levels comparable to those observed in young mice. This finding suggests that *D. pentandra* may help counteract age-related suppression of estrogen biosynthesis by enhancing steroidogenic activity in aging ovarian tissue. The observed effect may also reflect improved conversion of androgen precursors into estrogens under senescent conditions. Flavonoids and phenolic compounds have been reported to modulate steroidogenic and antioxidant pathways associated with ovarian function and estrogen biosynthesis, suggesting that the biological activities of *D. pentandra* may extend beyond passive phytoestrogenic effects.[8,14,21,24]

Estrogen receptors ERα and ERβ are key regulators of tissue responsiveness to estrogen and function as ligand-activated transcription factors controlling estrogen-dependent gene expression. Aging is associated with a progressive decline in the expression of both receptor subtypes, thereby impairing estrogen signaling capacity. [4,6,16] In the present study, aged mice exhibited significantly lower ERα and ERβ expression compared with young controls, whereas administration of *D. pentandra* extract increased the expression of both receptors in a dose-dependent manner. At the highest dose, ERα and ERβ expression approached or slightly exceeded the levels observed in young mice, suggesting improved estrogen signaling activity.

The concurrent upregulation of ERβ alongside ERα may be biologically relevant, as ERβ is known to modulate ERα-driven signaling and contribute to the maintenance of ovarian homeostasis. [4,6] This finding suggests that *D. pentandra* may promote a more balanced estrogenic environment rather than excessive activation of estrogen receptors. Flavonoids and lignans present in *D. pentandra* may contribute to these effects through phytoestrogenic or estrogen receptor–modulating activities, thereby enhancing estrogen signaling during reproductive aging. [14,25]

Collectively, the coordinated upregulation of StAR, aromatase (CYP19A1), ERα, and ERβ observed in this study indicates that *D. pentandra* exerts a multi-level modulatory effect on ovarian steroidogenesis and estrogen signaling during reproductive aging. Increased StAR and aromatase expression indicates restoration of key steroidogenic processes involved in estrogen biosynthesis, while concurrent upregulation of ERα and ERβ suggests improved tissue responsiveness to estrogen. These findings suggest that *D. pentandra* may function not only as a phytoestrogenic agent but also as a modulator of endogenous steroidogenic pathways that govern ovarian hormone production during aging.

These coordinated molecular alterations suggest that ovarian aging may involve interconnected impairment of steroidogenic activity and estrogen-responsive signaling pathways. Aging-associated oxidative stress and cellular dysfunction may contribute to reduced StAR and aromatase expression, thereby decreasing estrogen biosynthesis and weakening estrogen signaling through ERα and ERβ. The flavonoid-rich antioxidant compounds present in *D. pentandra* may help attenuate these alterations by reducing oxidative stress–related cellular damage and preserving ovarian hormonal regulation. This integrated modulatory mechanism may contribute to preservation of ovarian endocrine homeostasis during reproductive aging, as illustrated in Figure 2.

This study has several limitations. Circulating estrogen levels were not measured, and protein expression was assessed semi-quantitatively using immunohistochemistry. In addition, species differences may limit extrapolation of the findings to humans, and the specific bioactive compounds responsible for the observed effects of *D. pentandra* remain unidentified.

The present findings suggest that *D. pentandra* may have potential as a supportive botanical intervention for age-related ovarian endocrine decline. By enhancing the expression of key steroidogenic and estrogen–signaling markers, this extract may help maintain ovarian hormonal responsiveness during reproductive aging. Although clinical translation remains premature, these results provide preliminary molecular evidence supporting further investigation of *D. pentandra* as a candidate complementary approach for reproductive endocrine health in aging females.

Future studies are needed to evaluate circulating estrogen levels, ovarian functional outcomes, and fertility-related parameters following *D. pentandra* administration. Identification of the specific bioactive compounds responsible for the observed effects, as well as elucidation of the underlying molecular signaling

pathways, will be important to clarify the mechanism of action. In addition, long-term safety studies and translational investigations in higher animal models and humans are required before potential clinical application can be considered.

## CONCLUSION

This study demonstrates that *Dendrophthoe pentandra* (mango mistletoe) leaf extract significantly increased the expression of StAR, aromatase, ERα, and ERβ in aged mice, suggesting improved ovarian steroidogenic activity and estrogen signaling during reproductive aging. These findings suggest that *D. pentandra* may act as a potential phytoendocrine modulator and provide molecular insight into its possible role in supporting ovarian endocrine homeostasis during aging.

### Conflict of Interest

The authors report no competing interests.

### Acknowledgement

The authors gratefully acknowledge their indebtedness to the Faculty of Medicine, Universitas Brawijaya, for providing financial support and research facilities. The authors also thank the laboratory and animal facility staff for their technical assistance during the experimental procedures**.**

### Authors' Contributions

LI conceptualized the study, conducted the experiments, and drafted the manuscript. LRW contributed to data analysis and manuscript preparation. IAS. assisted with animal experiments and treatment administration. K provided conceptual guidance and critical input. WR performed immunohistochemical analyses. All authors reviewed and approved the final manuscript.

### Funding

This research was funded by the Faculty of Medicine, Universitas Brawijaya.

### Data Availability Statement

The data that supports the findings of this study can be obtained from the corresponding author upon reasonable request.

### Declaration of AI Usage in Scientific Writing

The authors declare that no artificial intelligence tools were used for data analysis or scientific interpretation. Any language refinements were carefully reviewed and approved by the authors, who take full responsibility for the manuscript's content.

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