

INHIBITORY EFFECT OF LUTEOLIN-7-METHYL ETHER ON ESTROGEN BIOSYNTHESIS IN HUMAN OVARIAN GRANULOSA CELLS VIA AROMATASE SUPPRESSION

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Relevance. Estrogens play a crucial role in breast development and various physiological processes. A key enzyme in estrogen biosynthesis is aromatase, which catalyzes one of the final steps in this process. In humans, aromatase expression is regulated by tissue-specific promoters, with the primary site of estrogen synthesis in premenopausal women being the ovaries, where its expression is driven by the activation of a proximal promoter.

To date, approximately 300 natural compounds, predominantly flavonoids, have been investigated for their effects on aromatase activity through cellular, non-cellular, and in vivo studies. This growing body of research highlights the potential of natural products as promising candidates for aromatase modulation.

Motherwort (*Leonurus* spp.) has a long history of medicinal use, with different species in Central Europe (*Leonurus cardiaca*) and Asia (*Leonurus japonicus* and *Leonurus sibiricus*)—traditionally employed in herbal medicine. In China, *L. japonicus* has been used for centuries to treat various gynecological conditions, including menoxenia, dysmenorrhea, amenorrhea, edema, oliguria, and ulcers. Nowadays, about 140 chemical constituents have been isolated and identified from this plant. However, the precise mechanisms underlying its pharmacological effects remain insufficiently explored. Further research is required to fully elucidate its potential as a novel therapeutic agent for the prevention and treatment of estrogen-dependent diseases.

The purpose of the study: To study the effect of luteolin-7-methyl ester on the biosynthesis of estrogen in human ovarian granulosa cells by inhibiting aromatase.

Materials and methods. The aboveground parts of *L. japonicus* were collected and 46 natural products have been isolated by extraction.

Results. Granulosa-like KGN cells of human ovaries were treated with the extracted XLY29 substance in various concentrations for 24 hours. XLY29 at 10 μm inhibited by about 70% the production of 17 β -estradiol in KGN cells compared to untreated cells. XLY29 also significantly inhibited forskolin-stimulated production of 17 β -estradiol and production of 17 β -estradiol, depending on concentration, with an IC₅₀ value of 5.213 $\pm$ 0.257 μm . Next, we investigated the tissue specificity of XLY29 in relation to the production of 17 β -estradiol. XLY29 also significantly inhibited the production of 17 β -estradiol in primary rat granulosa cells and human placental choriocarcinoma cells JEG3, but had no effect on estrogen biosynthesis in mouse osteoblasts. Also, XLY29 did not exhibit cytotoxicity in KGN cells at the concentrations studied. Further studies showed that XLY29 suppressed the biosynthesis of 17 β -estradiol depending on time. Inhibition of 17 β -estradiol production in KGN cells by XLY29 at 5 μm was first manifested after 12 hours and persisted until 48 hours, when the production of 17 β -estradiol was suppressed by about 50% compared with the control. In addition, biosynthesis of 17 β -estradiol resumed after removal of XLY29 for 12 hours, which suggests that inhibition of XLY29 estrogen biosynthesis is reversible. These results showed that XLY29 powerfully inhibits the biosynthesis of estrogen into KGN cells, depending on concentration and time.

Conclusions. In this study, we identified 46 structurally modified natural compounds isolated from *L. japonicus*. Among them, XLY29 was found to significantly downregulate aromatase expression.