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Therapeutic Effects of Phytoestrogen Naringenin in Polycystic Ovary Syndrome (PCOS): Involvement of Kisspeptin and Calcitonin Gene Related Peptide Signalling Pathways

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder and a major cause of infertility in women. Although studies have reported the effects of naringenin on PCOS; the underlying molecular mechanisms remain unclear. This study aimed to investigate the effect of naringenin on the expression of kisspeptin (*Kiss1*) and calcitonin gene-related peptide (*Cgrp*) genes in a rat model of PCOS.
Methods: Twenty female rats (180–200 g) were used in this study. To PCOS induction, two mg of estradiol valerate was injected intramuscularly (IM) per rat. The control and PCOS groups received saline, while the other two groups were treated intraperitoneally with naringenin at either 20 mg/kg or 50 mg/kg, respectively. Subsequently, hypothalamic tissue was collected, and gene expression levels were analyzed using real-time PCR.
Results: The expression *Kiss1* and *Cgrp* genes increased significantly in the PCOS group contrasted to the control ($p \leq 0/05$). In the groups treated with naringenin, the levels of *Kiss1* and *Cgrp* gene expression reduced significantly compared to the PCOS group ($p \leq 0/05$).
Conclusion: Naringenin may ameliorate PCOS by downregulating hypothalamic *Kiss1* and *Cgrp* gene expression in rats. These results suggest a novel mechanism of naringenin's action and highlight its potential for clinical application.

Keywords: Calcitonin gene-related peptide, Kisspeptin, Narengenin, Polycystic ovary syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial disorder involving genetic, endocrine, and metabolic factors. PCOS is a primary cause of infertility, affecting 5–10% of women of reproductive age (1). The condition is characterized by primary abnormalities in the hypothalamic-pituitary-gonadal (HPG) axis, which lead to increased gonadotropin-releasing hormone (GnRH) frequency and luteinizing hormone (LH) pulsatile secretion. These disruptions contribute to a range of metabolic disorders, including insulin resistance, ovarian dysfunction, and excessive ovarian androgen production (2). Current treatment modalities for PCOS include adopting a healthy lifestyle with regular exercise, laparoscopic ovarian surgery, and pharmacological therapies such as glucocorticoids, tamoxifen, clomiphene citrate, aromatase inhibitors, and metformin

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(1). However, due to the severe adverse effects of these medications, identifying alternative treatments is essential for minimizing negative side effects.

Kisspeptin is a product of the Kiss1 gene. In the brain, the major product of the Kiss1 gene is a 54-amino acid peptide that exerts its biological activity by binding to the GPR-54 receptor (3). Within the brain, two key hypothalamic nuclei, the anteroventral periventricular nucleus (AVPV) and the arcuate nucleus (ARC), are the primary sites of kisspeptin synthesis. In peripheral tissues, kisspeptin expression has been reported predominantly in the ovary, testis, adipose tissue, and placenta (4,5). Evidence indicates that kisspeptin plays a vital role in regulating mammalian reproduction, including the secretion of GnRH and gonadotropins, the onset of puberty, and ovulation (6). In individuals with PCOS, kisspeptin levels are elevated, leading to increased stimulation of the hypothalamic-pituitary-gonadal (HPG) axis activity (7).

Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide that belongs to the calcitonin superfamily. CGRP is encoded by the calcitonin gene, along with calcitonin (CT). There are two types of CGRP: CGRP1 and CGRP2. CGRP1 is derived from the α-calcitonin gene-related peptide, whereas CGRP2 is derived from the β-calcitonin gene-related peptide (8). CGRP is widely distributed in the central nervous system, including the cerebral cortex, locus coeruleus, parabrachial nucleus (PBN), hypothalamic nuclei, and amygdala, as well as in peripheral organs such as the ovary, lung, pancreatic islets, adipocytes, and cardiac fibroblasts. It plays a role in regulating vascular tone, wound healing, inflammatory responses, pain, diabetes, and obesity (8, 9). Studies indicate that CGRP influences the reproductive axis by suppressing GnRH release (10). Elevated CGRP levels have been observed in individuals with PCOS (11).

Naringenin (4',5,7-trihydroxyflavanone) is a phytochemical compound primarily found in citrus fruits (including grapefruits and oranges) and tomatoes. It exhibits various pharmacological effects, including hepatoprotective, anticancer, antioxidant, antidiabetic, and aromatase-modulating properties (12). Evidence suggests that naringenin also possesses steroidogenic activity and can improve ovarian function in patients with polycystic ovary syndrome (13). Although the antioxidant and inhibitory effects of naringenin on the hypothalamic-pituitary-gonadal axis have been demonstrated in PCOS (14), the molecular mechanisms underlying its suppressive effects on testosterone secretion remain unclear. Therefore, this study aimed to investigate the impact of naringenin on the gene expression of neuropeptides upstream of GnRH neurons, specifically *Kiss1* and *Cgrp*, in the hypothalamus of a PCOS rat model.

Materials and Methods

Animal

The rats were taken care of in the laboratory environment for two weeks for adaptation, where the cycle was 12-h light/12-h dark. The temperature of the laboratory environment was maintained at 22 ± 2 °C.

PCOS induction

To determine the phase of estrous, vaginal smears were performed over two weeks. To induce PCOS, estradiol valerate (Cas No. 50-28-2, Co., USA) (2 mg per rat) in 0.2 mL of sesame oil (Barij Pharmaceutical, Iran) was administered via intramuscular injection. Vaginal smears were then conducted every 15 days. Sixty days after the estradiol valerate injection, PCOS was confirmed by observing persistent cornified epithelial cells under a light microscope (15).

Animal group and treatment

To perform the experiment, female Wistar rats (180–200 g) were divided into groups (n = 5). The injection was administered intraperitoneally for 14 days at 8-9 AM, at 8–9 AM. The control and PCOS groups received saline, while one PCOS group was treated with 20 mg/kg naringenin (Cas No. 67604-48-2, Co.,

USA) and another received 50 mg/kg naringenin. After the treatment period, the hypothalamus was removed and immediately stored at -80 °C.

RT-PCR protocol

Hypothalamic tissue was homogenized for RNA extraction. RNA was isolated using the TRIzol kit and its concentration was determined with a Nanodrop. cDNA was synthesized from 1 µg of RNA according to the instructions of the kit (Biotech rabbit, Germany). The RT-PCR reaction was performed using SYBR Green Master Mix according to the protocol of the kit (Takara, Japan). The real-time PCR cycling conditions were as follows: an initial denaturation step at 95 °C for 15 min, followed by 40 cycles of denaturation at 95 °C for 20 sec, annealing at 60 °C for 15 secs, and extension at 72 °C for 10 secs. The forward and reverse primer sequences used are listed in Table 1. Changes in gene expression were calculated using the $2^{-\Delta\Delta CT}$ equation.

Statistical analysis

The analysis of the data was conducted using SPSS software (version 16) and one-way ANOVA. To evaluate significant differences among the groups, Tukey's post hoc test was performed. The results were presented as mean ± SEM and statistical significance determined at $P \leq 0.05$.

Table 1. Sequence of sense and antisense primers.

Genes	Primer	Sequences	PCR product size (bp)
kiss-1 (NM_001412625.1)	forward	5′- TGATCTCGCTGGCTTCTTGGC -3′	98
	reverse	5′- GGGTTCAGGGTTCACCACAGG -3′	
Cgrp (XM_008759676.4)	forward	5′- TCTAAGCGGTGTGGG AATCT -3′	155
	reverse	5′- TAGGGGTGGTGGTTTGTCTC -3′	
GAPDH (NR_197270.1)	forward	5′- AAGTTCAACGGCACAGTCAAG -3′	120
	reverse	5′- CATACTCAGCACCAGCATCAC -3	

Results

The results showed that the mRNA level of *Kiss1* increased significantly in the PCOS group compared to the control ($P \leq 0.05$) (Fig. 1). Naringenin injection (20 or 50 mg/kg) decreased the mRNA level of *Kiss1* compared to the PCOS group. The reduction in both the 20 mg/kg and 50 mg/kg treatment groups was statistically significant ($P \leq 0.05$).

A significant increase in the mRNA level of *Cgrp* was observed in the PCOS group compared to the control ($P \leq 0.05$) (Fig. 2). In the group receiving 20 mg/kg of naringenin, the level of *Cgrp* gene expression did not decrease significantly compared to the PCOS group. However, in the group treated with a dose of 50 mg/kg of naringenin, there was a significant decrease in the mRNA level of *Cgrp* ($P \leq 0.05$) (Fig. 2).

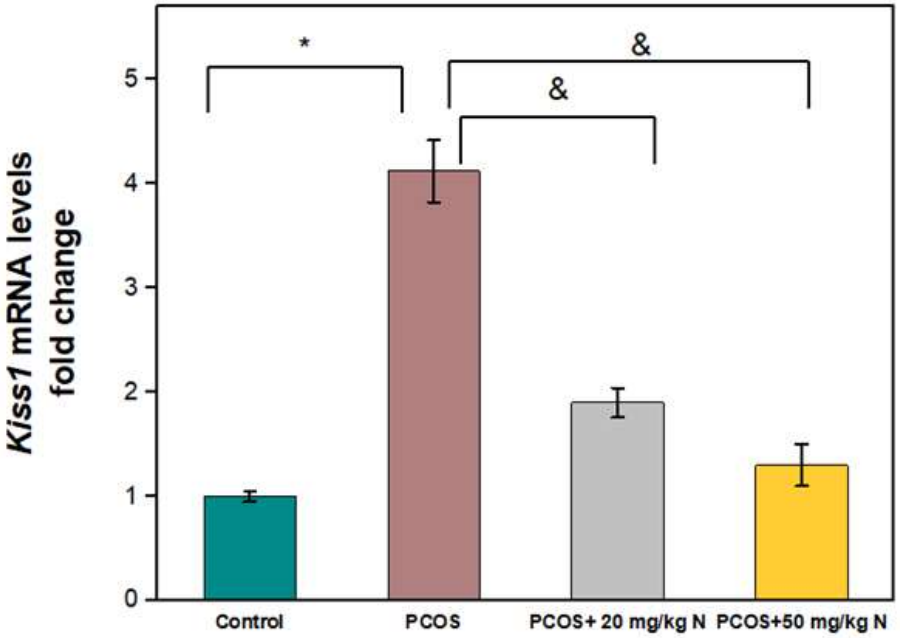

Fig. 1. The effects of naringenin on the *Kiss1* gene expression in a rat model of PCOS. The results are expressed as mean ± SEM and significance was defined by $^{*}P \leq 0.05$. *: compared with control; &: compared to the PCOS group.

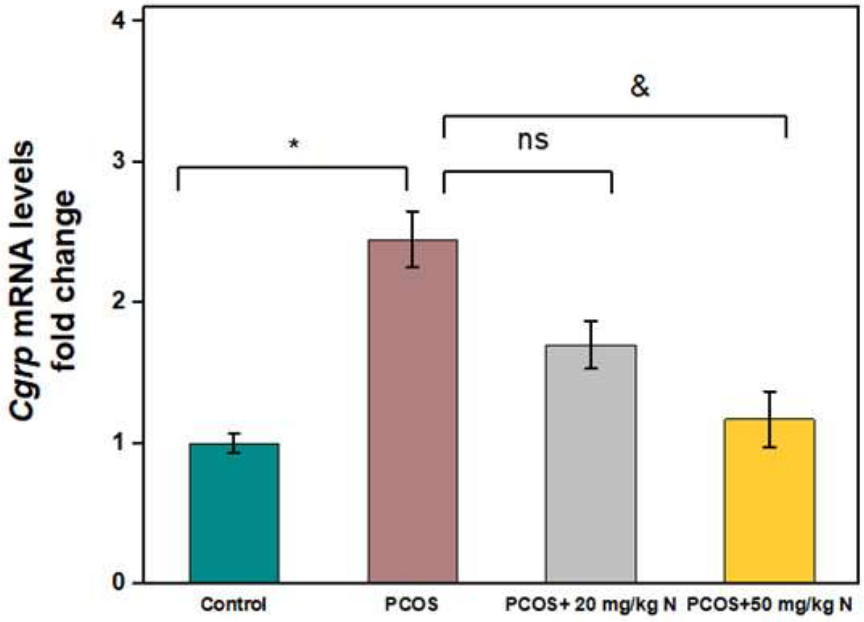

Fig. 2. The effects of naringenin on the *Cgrp* gene expression in a rat model of PCOS. The results are expressed as mean ± SEM and significance was defined by $^{*}P \leq 0.05$. *: compared with control; &: compared to the PCOS group.

Discussion

The present study showed that Kiss1 gene expression in the PCOS group was higher compared to the control group. However, the small sample size means the findings should be considered preliminary and ideally followed up with larger studies.

Previous studies have also reported an increase in *Kiss1* gene expression in PCOS (16). Various signaling pathways are involved in the regulation of kisspeptin synthesis. The Kiss1/GPR54 signaling system is vital for reproduction and is one of the best-defined systems that conveys gonadal hormone signals to initiate puberty. The primary sites of its synthesis are the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV) of the hypothalamus, which interact

with GnRH neurons. Kisspeptin signals GnRH neurons, stimulating GnRH secretion (17). Studies suggest that changes in *kisspeptin* gene expression may be mediated by adiponectin (18). The presence of adiponectin receptors on GnRH neurons and its inhibitory effect on GnRH release highlight its important role in the hypothalamic-pituitary-gonadal (HPG) axis (19). Additionally, adiponectin levels are decreased in PCOS patients (20). Adiponectin is also known to inhibit hypothalamic *Kiss1* gene expression (18). Previous studies have indicated that naringenin treatment increases both adiponectin secretion and its receptor expression (21, 22). Furthermore, naringenin is a phytoestrogen structurally similar to β-estradiol (23) and can act on both α and β-estrogen receptors (24). It has also been reported that naringenin stimulates aromatase activity, leading to increased estrogen levels (25). Additionally, naringenin has been observed to improve ovarian function (13). Our results showed that in PCOS model rats treated with naringenin, *Kiss1* gene expression decreased. Therefore, the reduction in Kiss1 gene expression by naringenin is likely mediated by increased adiponectin levels in PCOS rats.

Another mechanism by which naringenin reduces the expression of the *Kiss1* gene may involve the dopaminergic neurotransmitter system. Dopamine is produced in several brain regions, including the substantia nigra and hypothalamus, and exerts its effects through receptors (D1–D5). Dopaminergic signaling is known to modulate various physiological processes, including the regulation of reproductive functions. Studies have shown that dopaminergic input can directly influence kisspeptin neurons. For instance, dopamine can modulate the activity of kisspeptin-expressing neurons in the arcuate nucleus (ARC), affecting their firing rate and kisspeptin release (26, 27). It has been reported that the activation of D2 receptors can inhibit *kisspeptin* expression, leading to decreased GnRH release and subsequent reductions in LH and FSH levels (28). Naringenin influences the synthesis and release of dopamine and has been found to increase dopamine levels (14). Therefore, naringenin may decrease *Kiss1* gene expression in PCOS rats by enhancing the dopaminergic system activity.

Previous studies have shown that CGRP is involved in the pathology of PCOS, with elevated levels observed in PCOS patients (29). These findings align with those of the present study, which also indicate an increase in *Cgrp* gene expression in PCOS. Androgens play a key role in the pathophysiological processes of PCOS, a common endocrine disorder affecting women of reproductive age. They exert their effects through androgen receptors, which are present in various tissues, including the brain and ovaries. The activation of these receptors can influence the expression of neuropeptides such as CGRP. Since androgen levels are elevated in women with PCOS (30), hyperandrogenism may be one reason for the increased *Cgrp* gene expression observed in PCOS rats. Several studies have demonstrated that testosterone administration upregulates Cgrp gene expression in rats (31, 32). Additionally, CGRP receptors are expressed in human granulosa cells, and exogenous CGRP administration has been shown to enhance testosterone release from these cells (11). Furthermore, CGRP plays a crucial role in suppressing GnRH and luteinizing hormone (LH) pulses in rats (33). Evidence suggests that naringenin has anti-androgenic effects, as it reduces androgen levels in PCOS rats (34). In the present study, naringenin administration decreased *Cgrp* gene expression in PCOS model rats. Therefore, it is possible that naringenin downregulates *Cgrp* gene expression by lowering androgen levels.

There is a close interaction between the GABAergic system and CGRP. Gamma-aminobutyric acid (GABA) plays an important role in reproductive activities, exhibiting inhibitory effects on the activity of GnRH neurons (35, 36). Additionally, evidence suggests that GABA regulates CGRP. GABAergic neurons receive inputs from CGRP-expressing neurons and can inhibit the

activity of CGRP neurons, an effect mediated through $GABA_A$ receptors (37, 38). Naringenin, a citrus-derived compound, can cross the blood-brain barrier and exerts various effects on the central nervous system. It acts on the benzodiazepine-binding site of the GABA receptor, thereby modulating the activity of neurons in the brain (39). In the present study, naringenin reduced the expression of the *Cgrp* gene in PCOS model rats, suggesting that this downregulation may result from naringenin's stimulatory effect on the GABAergic system.

Briefly, the induction of PCOS caused a significant increase in hypothalamic mRNA levels of *Kiss1* and *Cgrp*. Naringenin may downregulate the expression of *Kiss1* and *Cgrp* in PCOS rats. Investigating the role of naringenin in reproductive regulation could be valuable for identifying alternative treatments for reproductive disorders associated with hyperactivity of the HPG axis.

Ethical statement

The University of Mohaghegh Ardabili's Research Ethics Committee oversaw the study's execution (code: IR.UMA.REC.1402.076)

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Conflict of Interests

There is no conflict of interest in this article.

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Authors' contribution

Literature search and data collection were performed by FM and HM and HKH. The first draft of the manuscript was written by HM and HKH. FM and HKH supervised the work and FM conceptualized the study. All authors read and approved the final manuscript.

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