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Ameliorative effects of curcumin on dehydroepiandrosterone-induced polycystic ovary syndrome in female rats

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Abstract

Polycystic ovarian syndrome (PCOS) is one of the most common hormonal disorders women experience during their reproductive life. This study aims to evaluate the potential beneficial effects of curcumin in polycystic rats induced by dehydroepiandrosterone. A total of forty female rats weighing 300±20 g was used. The rats were distributed into four groups (n=10), with the first group (GI) receiving sesame oil, the second group (GII) administered curcumin orally 200 mg/kg, and the third group (GIII) injected i.p. with 6 mg/100g dehydroepiandrosterone daily for 21 days, PCOS is the result of an extended length of time. Fourth group (GIV) administrated DHEA 6 mg was administered for 21 days, followed by 200 mg/kg curcumin for 14 days. Blood samples were collected at the end of the experiment. The levels of serum testosterone, FSH, LH concentrations, progesterone, estradiol, leptin, and ghrelin were measured, and fasting blood glucose (FBG) and fasting serum insulin (FSI) were measured to calculate HOMA-IR. In comparison to the control group, the serum levels of LH, FSH, and testosterone, as well as the HOMA-IR index and leptin, increased significantly in the GI DHEA-treated group, while progesterone, estradiol, and ghrelin levels declined. Curcumin, on the other hand, reduced DHEA's adverse effects, as seen by lower serum levels of LH, FSH, and testosterone, as well as lower HOMA-IR index and leptin, and greater levels of progesterone, estradiol, and ghrelin in the GIV group. In conclusions; it may be inferred that curcumin reduces the negative consequences of PCOS, and it is suggested that curcumin be used to treat PCOS patients.

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Introduction

PCOS is a complicated disease involving endocrine reproductive and metabolic disorders resulting in human and animal anovulation (1). According to various diagnostic criteria, the morbidity rate of PCOS in women ranges between 6-20 %, and the mechanism through which PCOS may happen is still elusive. Insulin resistance is a possible mechanism responsible for PCOS (2). About 50% of women with PCOS suffer from insulin resistance, a known cause of hyperinsulinemia (3). Kayampilly and Menon found that increased levels of DHT in ovarian granulosa cells selectively inhibited the mitogenic actions of insulin through the MAPK signaling while exerting no effect on it signaling through the Akt pathway (4). The metabolic response to insulin activity, which includes the PI3K pathway, has proven faulty in such circumstances (5). Several typical hormone treatments are employed to treat PCOS and stimulate ovulation. Arthritis, joint or muscle discomfort, and psychological disorders are among the side effects of this therapy (6). There is a high interest in safe and effective natural medicines. Several herbal treatments have been explored on PCOS-affected people and animal models (7). Curcumin, a natural component of turmeric, contains biological properties such as anti-inflammatory, antioxidant, hypoglycemic, and anti-hyperlipidemic properties (8,9).

Curcumin has beneficial effects and can protect ovarian oocytes from oxidative stress by increasing tissue antioxidant levels (10). Curcumin has been shown to alleviate endometriosis in vitro and in vivo investigations through anti-inflammatory, anti-proliferative, anti-angiogenic, and proapoptotic pathways (11).

To our knowledge, the effect of Curcumin on HOMA-IR in animals with induced PCOS has not been studied yet. However, this research aimed to evaluate the changes in hormones of reproductive and insulin metabolism (via measurement HOMA-IR) that may occur in female rats with DHEA-induced PCOS and to assess the ability of curcumin to cure PCOS.

Materials and methods

Ethical approval

The study's methodology was authorized by the Scientific and Ethical Committee of the College of Pharmacy, University of Kerbela, and the approval reference number for this research is 2021An.35on November 2021.

Experimental animals and treatment

Forty female rats weighing 300±20 g was employed. All animals were reared in metal cages with food and water ad libitum and kept in a 25°C environment with a 12:12 h light: dark cycle. The rats were divided into four groups (n=10), with the first (GI) receiving sesame oil, the second (GII) administered Curcumin orally 200 mg/kg (12), and the third (GI) injected i.p. with 6 mg dehydroepiandrosterone (DHEA) per 100 g day for 21 days (DHEA dissolved in 0.2 mL sesame oil) (DHEA, Sigma-Aldrich (Shanghai) Trading Co., Ltd). PCOS is caused by a period (13). The fourth group (GIV) was given DHEA 6 mg for 21 days and 200 mg/kg of Curcumin for 14 days. Sigma Chemicals Co. provided the curcumin. In St. Louis, Missouri, and was dissolved in 0.5 percent carboxymethylcellulose for each month for 30 days, superabsorbent biopolymer; carboxymethyl cellulose (CMC) was used as an emulsifier for curcumin, which is a turmeric derived water insoluble polyphenolic compound with antibacterial/anti-cancer properties (14). Blood samples were collected through cardiac puncture at the end of the experiment. The serum was isolated and frozen at -20ºC until the following indicators could be tested.

Hormonal assay

The levels of serum testosterone, FSH, LH concentrations, progesterone, estradiol, fasting blood glucose (FBG) and fasting serum insulin (FSI) (HOMA-IR), leptin, and ghrelin were measured using commercial ELISA kits (American Laboratory Products Company (ALPCO), USA by the manufacturer's guidelines.

Evaluation of IR

The fasting blood glucose (FBG) and fasting serum insulin (FSI) levels were determined using blood samples. FBG was measured using a glucose oxidase method, and FIS was calculated using an enzyme-linked immunosorbent assay (ELISA) kit that was directly competitive (15). A microplate reader was used to read the optical readings in the 450 nm range, and the homeostasis model assessment index was used to calculate insulin resistance (HOMA-IR), the following formula was used to compute: (fasting insulin - fasting glucose)/22.5.

Statistical analysis

All data was statistically examined using the Social Sciences Statistical Package (SPSS version 19). Least significant differences (LSD) were used to identify the significance of the differences between means, and P values less than 0.01 were considered significant. One-way analysis of variance (ANOVA) was used to compare between study groups. The average of the obtained results was expressed as the mean ± standard error.

Results

The results in table 1 clarified there was a significant increase in the serum of LH, FSH, and Testosterone. At the same time, Progesterone level and estradiol decreased in GIII treated with DHEA compared to GII administered curcumin and control group. In contrast GIV group reduced the deleterious effect of DHEA compared to GIII.

Table 1: Effect of Curcumin on the hormonal levels of PCOS female rats

Group	LH (µIU/ml)	FSH (µIU/ml)	Progesterone (pg/ml)	Testosterone (ng/ml)	Estradiol (pg/ml)
GI	2.58±0.19 ^{a}	3.10±1.21 ^{a}	121.88±12.57 ^{a}	9.71±0.71 ^{a}	131.14±10.23 ^{a}
GII	1.73±0.26 ^{a}	2.41±1.31 ^{a}	139.24±14.66 ^{a}	12.13±0.12 ^{a}	139.91±12.44 ^{a}
GI	8.04±0.15 ^{b}	8.22±0.71 ^{b}	109.41±12.31 ^{b}	7.32±0.29 ^{b}	103.31±11.32 ^{b}
GIV	3.14±0.33 ^{ac}	5.33±0.75 ^{ac}	118.32±9.12 ^{ac}	8.96±0.15 ^{ac}	121.72±9.66 ^{ac}
LSD	1.13	1.87	9.26	0.88	9.93

By measuring fasting blood insulin and glucose and computing the HOMA-IR index, we explored IR in PCOS model rats. Table 2 shows there was a significant increase in HOMA-IR index in the HEA treated group in comparison with GII administered Curcumin and control group, in contrast to the GI treated group, the results in the table 2

demonstrated a substantial decrease in the HOMA-IR index in the GIV with curcumin-treated group. Also, the results in table 2 showed an enhanced level of leptin, as well as a lower level of ghrelin in the DHEA-treated group in comparison with the GII, administered curcumin, and control group. Furthermore, the data in table 2 revealed a significant decrease in the level of leptin also an increase in the level of ghrelin in the DHEA with curcumin-treated group compared to the GI treated group.

Table 2: Effect of curcumin on the HOMA-IR, leptin, and ghrelin levels of PCOS female rats.

Group	HOMA-IR	Leptin	Ghrelin
GI	2.7±0.56 [a]	28.38±3.87 [a]	0.64±0.05 [a]
GII	2.6±0.87 [a]	25.86±4.23 [a]	0.68±0.01 [a]
GI	9.9±1.44 [b]	47.71±9.56 [b]	0.24±0.06 [b]
GIV	3.83±1.06 [ac]	32.73±5.37 [ac]	0.54±0.08 [ac]
LSD	1.09	6.26	0.13

Discussion

One of women's most frequent and complex reproductive illnesses is polycystic ovary syndrome (PCOS) (16,17). Hyperandrogenism, polycystic ovaries, and anovulation are all symptoms of this condition (18). The diagnosis is based on three clinical signs: no ovulation, elevated levels of androgens, and several tiny cysts (19). Excessive androgenic hormone production in the ovaries caused by the pathophysiology of PCOS is frequently associated with an excess of luteinizing hormone (LH) from the anterior pituitary gland or a high level of insulin in the blood, either alone or in combination (20). Insulin resistance (IR) and obesity affect most females with PCOS (21). Besides, pending the creation of follicular cysts, estrous cycle disruption, abnormal ovarian steroidogenesis, and anovulation, serous estradiol decreases and has a causal relationship connected to hyperandrogenism in PCOS patients and the DHEA-induced illness model of an animal (22).

These findings supported those who stated that DHEA promotes PCOS by interfering with hormones regulating androgen balance, glucose homeostasis, and follicular growth. DHEA has been proven to boost the production of LH in the brain and pituitary gland (23), Which is consistent with our findings. This could raise estrogen levels, one of PCOS's most noticeable symptoms (24). In this investigation, DHEA administration dramatically boosted plasma testosterone levels in female rats. Compared to the control rats, plasma progesterone levels in the DHEA-treated animals were comparatively low. This drop in plasma progesterone levels in DHEA-treated rats could result from anovulation (25).

Insulin resistance and hyperinsulinemia are essential factors in the development of PCOS, which is linked to a higher risk of abdominal obesity and metabolic syndrome than the general population; DHEA enhanced IR and slows down the estrous cycle; according to another research, hyperinsulinemia is a consequence of PCOS, characterized by a connection between high serous insulin and IR (26).

DHEA increases androgen production compared to the control group, which may cause insulin resistance through raised FBG, HbA1c, fasting plasma insulin levels, and an enhanced HOMA-IR index (27). These findings corroborated previous research (21), which claimed that DHEA caused PCOS by affecting hormones involved in androgen balance, glucose homeostasis, and follicular development regulation. PCOS-affected rats in this investigation had increased FIS, FBG, and HOMA-IR levels. IR causes hyperglycemia. However, PCOS' specific mechanism is unknown (24).

Compared to other groups, the results showed an enhanced level of leptin and a lower level of ghrelin in the (GI) DHEA-treated group. Leptin, which is produced by the "obesity." A signal is a gene that the body is storing enough fat (28). At the hypothalamic level, leptin plays a role in the reproductive system by acting as a permissive signal to reproductive processes. It acts as a counter-signal to ghrelin (29). It's thought to be a relationship between nutrition and reproduction (30). Leptin has been found to work as an energy-balancing hormone, causing a reduction in calorie consumption and an increase in energy expenditure (31). As a result, leptin regulates the breakdown of energy sources such as lipids and carbs (32). Insulin resistance causes a rise in serum insulin levels, stimulating leptin mRNA production in adipocytes and raising circulating leptin levels (33). The PCOS group had greater serum leptin levels than the other groups in our study. These findings are consistent with those of Telli *et al.* (34), who found that the blood leptin level in obese PCOS patients was considerably more significant than in controls. Ghrelin is another peptide hormone that affects energy balance, food intake, and body mass regulation. It plays an essential function: blood concentration rises before a meal and declines after food consumption, and it helps regulate hunger in the short term by increasing food intake (35). Previous research has found that women with PCOS have reduced ghrelin levels in their blood (36). Most minor Ghrelin levels in the blood have been associated with a positive energy balance, such as obesity, and are thus inversely related to insulin resistance and type 2 diabetes (37). Furthermore, it has previously been demonstrated that an increase in insulin concentration causes a decrease in serum ghrelin concentration (38). This could point to a link between insulin sensitivity and ghrelin; after all, insulin is thought to play a vital role in ghrelin secretion and feedback control (39).

Curcumin reduced the harmful effect of DHEA, as seen by lower serum levels of LH, FSH, and testosterone, as well as higher levels of Progesterone and Estradiol in the (GIV)treated group compared to the (GIII)treated group and

control group. It has several impacts, including raising progesterone levels, which is necessary for females to have a regular ovarian cycle, and regulating the corpus luteum activity (40). Curcumin lowers testosterone levels and Alters progesterone and androgen production (41). Curcumin, as a phytoestrogen (42), can interact with steroid hormones and their receptors, influence the hypothalamo hypophysial hypophysial ovarian axis, and treat some reproductive disorders (43). Curcumin, for example, can suppress androgen receptors and stimulate 3-beta-hydroxysteroid dehydrogenase in mouse ovaries (44), but it does not affect aromatase (45). Curcumin also reduced the impact of dehydroepiandrosterone on ovarian cell apoptosis in mice; Curcumin's influence on ovarian functions and state may thus be mediated by its action on ovarian steroid hormone receptors (46).

On the other hand, Curcumin improves IR by affecting the expression of GLUT4 and ER, which are involved in glucose metabolism (47). The insulin signaling pathway is required for GLUT4 transformation on the cell surface (48), and IR reduces GLUT4 expression (49). Curcumin administration has been proven to help with obesity, diabetes, metabolic syndrome, and cardiovascular disease, which can all be prevented by reducing body weight, insulin resistance, and abnormal lipid levels (50).

An increase in the level of ghrelin in the (GIV) DHEA with curcumin-treated group. This is in agreement with (51). Curcumin use can help weight loss and metabolic health by boosting basal metabolic rate like other natural products (52), leading to higher energy expenditure (53). It interacts directly with adipocytes and immune system macrophages, helping reduce leptin resistance, enhance adiponectin, and reduce inflammatory indicators linked to obesity, such as leptin, ghrelin, and resistin (54). Obesity is connected to a variety of metabolic and non-metabolic disorders, including CHD, T_2DM, and PCOS, as indicated by studies that found curcumin consumption was linked to BMI, weight circumference, and leptin levels all dropped significantly (55). Curcumin Because adipocytes release leptin, a decrease in leptin secretion is related to lipolysis increases. Leptin levels have been closely linked to the body's total quantity of white fat (56).

Conclusion

Our findings suggest curcumin may have an Ameliorative effect on PCOS. As a result, oral administration of curcumin as a traditional medicine appears to be beneficial in treating PCOS.

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Conflict of interests

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التأثيرات التحسينية للكركمين على متلازمة المبيض المتعدد الكيسات التي يسببها ديهيدروبياندروستيرون في إناث الفئران

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الخلاصة

متلازمة المبايض المتعددة الكيسات هي إحدى الاضطرابات الهرمونية الأكثر شيوعا التي تواجهها النساء خلال حياتهن الإنجابية. يهدف هذا البحث إلى تقييم التأثيرات الإيجابية المحتملة للكركمين في الجرذان ذات المبايض المتعددة الكيسات التي تم معالجتها بواسطة الديهيدروإيبياندروستيرون. تم استخدام مجاميع مكونه من أربعين جرذ إناث يبلغ وزنها ٣٠٠ ± ٢٠ غم. تم توزيع الجرذان إلى أربع مجموعات بواقع عشرة جرذان للمجموعة الواحدة (حيث تلقت المجموعة الأولى زيت السمسم، وأعطيت المجموعة الثانية كركمين عن طريق الفم بمقدار ٢٠٠ ملغم/كغم، وتم حقن المجموعة الثالثة تحت الجلد بمقدار ٦ ملغم/١٠٠ غم من الديهيدروإيبياندروستيرون يوميا لمدة ٢١ يوما. في حين تم إعطاء المجموعة الرابعة الديهيدروإيبياندروستيرون بمقدار ٦ ملغم لمدة ٢١ يوما، تليها ٢٠٠ ملغم/كغم من الكركمين لمدة ١٤ يوما. تم جمع عينات الدم في نهاية التجربة. قيست مستويات التستوستيرون والهرمون المنشط للمبيض والهرمون الحليبي والبروجيستيرون والاستراديول واللبتين والغريلين في المصل، وقيست سكر الدم عند الصيام (تحليل السكر الصائم) والإنسولين في المصل عند الصيام (تحليل الأنسولين الصائم لحساب (تحليل مقاومة الأنسولين). في مقارنة مع المجموعة الضابطة، ارتفعت مستويات الهرمونات المنشطة للمبيض والهرمون المنشط للمبيض والتستوستيرون في المصل بالإضافة إلى مؤشر تحليل مقاومه الأنسولين واللبتين بشكل كبير في المجموعة التي تمت معالجتها في المجموعة الأولى الديهيدروإيبياندروستيرون، في حين انخفضت مستويات البروجيستيرون والاستراديول والغريلين. على النقيض من ذلك، قلل الكركمين من التأثيرات الضارة للديهيدروإيبياندروستيرون، كما هو واضح من خلال انخفاض مستويات الهرمونات المنشطة للمبيض والهرمون المنشط للمبيض والتستوستيرون في المصل بالإضافة إلى انخفاض مؤشر تحليل مقاومه الأنسولين واللبتين، وزيادة مستويات البروجيستيرون والاستراديول والغريلين في مجموعة الرابعة في الخلاصة، يمكن استنتاج أن الكركمين يقلل من العواقب السلبية لـ متلازمة المبايض المتعددة الكيسات، ويقترح استخدامه لعلاج مرضى متلازمة المبايض المتعددة الكيسات.