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Studying the Effect of Curcumin (Standard & Supplements) and Zinc on the Concentrations of Glucose, Insulin, HOMA-IR, and Anti-Mullerian Hormone in PCOS-Model Rats

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Abstract

The goal of the current study was to investigate the effects of curcumin in both formulas (supplement and standard), zinc, and then use them together to show their effect on the levels of glucose, insulin, insulin resistance (IR), and anti-mullerian hormone (AMH) in the model of female rats with induced polycystic ovary syndrome (PCOS) using 1mg/kg/day of letrozole for 21 days followed by a treatment period of 14 days including different treatments of zinc 30 mg/kg, curcumin standard 200 mg/kg, curcumin supplement 200 mg/kg, (curcumin standard plus zinc), (curcumin Supplement plus zinc) and metformin as a standard treatment. After the treatment, all female rats were sacrificed, and blood samples were collected from the inferior vena cava of each rat for biochemical measurements. The concentrations of insulin and AMH were measured by using of immunoassay technique ELISA. Glucose was determined by using the spectrophotometric method while insulin resistance is measured by calculation methods. The results indicate that the administration of letrozole as an aromatase inhibitor resulted in a significant elevation of anti-mullerian hormone (AMH), glucose, insulin, and insulin resistance in the polycystic ovary syndrome-designed model. Curcumin (standard or supplement) and zinc showed a significant decrease in insulin levels in all treatment groups, while the effect was more pronounced when zinc was taken with a curcumin supplement. Results also showed a significant decrease in glucose and IR, this indicates the ability of curcumin supplement and zinc to restore glucose and IR to their normal level in the healthy control group. Anti–mullerian hormone decreased significantly for all groups that took both forms of curcumin, and curcumin and zinc together, while the decrease was highly significant in curcumin supplement and zinc.

Keywords: Anti-Mullerian Hormone (AMH), Curcumin (Cur), Insulin, Resistance (IR), Polycystic Ovary Syndrome (PCOS), Zinc.

Introduction

Polycystic Ovarian Syndrome, also known as PCOS, is an endocrine condition that affects reproductive aged-women. The prevalence of PCOS varies from 5% to 15%, depending on the diagnostic criteria [1]. Stain and Leventhal were the first scientists who mentioned and explained the relation between amenorrhea, hirsutism, and enlarged PCO [2]. Polycystic ovary syndrome (PCOS) is accompanied by hyperandrogenism, menstrual disorder, infertility, and hirsutism [3].

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PCOS is related to metabolic problems including obesity, resistance to insulin (IR), impaired glucose tolerance, exposure to diabetes, hypertension, and disturbance in lipid profile, metabolic syndrome, nonalcoholic fatty liver disease, and risk of cardiovascular disease [4]. Elevated inflammatory indicators, oxidative stress levels, and androgens (LH), reduced the level of follicle-stimulating hormone. FSH and estrogen have been identified in females that have PCOS same thing has been shown in the animal models of PCOS [5]. Polycystic ovary syndrome (PCOS) is a common reason for infertility [6]. The exact pathophysiology of PCOS is not completely explained yet [7]. Furthermore, fatness showed irregular reproductive function in women leading to infertility. In addition, it has been presented that insulin resistance and increased testosterone level are enhanced in PCOS women who reduce 5% of their original weight, which appear to be essential relatives to PCOS pathogenesis [8]. Polycystic ovarian syndrome and hormonal disorders are common reasons for infertility [9]. However, there are numerous explanations for irregular ovarian function in females with PCOS. Pathophysiological anomalies in gonadotropin secretion, ovarian folliculogenesis, steroidogenesis, diminished insulin secretion, and dyslipidemia, have also been termed PCOS. In women with PCOS, altered hypothalamus and pituitary increase gonadotropin excretion of luteinizing hormone (LH), and raised the level of androgen production from the ovarian theca cells, which leads to hyperandrogenism. Also, follicles within the ovary have an increased resistance to follicle-stimulating hormone[4]. It has been shown that herbal components can have a significant improvement in some disorders of PCOS. Several studies on the causes of PCOS about traditional herbal and non-chemical treatments [5]. Nowadays there are different pharmaceutical treatments have been proposed for PCOS. However, the side effects of these treatments have different impacts. The greatest of them may moderately recover metabolic and hormonal irregularities. This may be a realistic approach intended for avoiding and improving PCOS by affecting the features elaborate in the disease [10]. The traditional treatment of PCOS includes insulin sensitizers and anti-androgen drugs. These drugs have many assistances but cause health trouble [11].

Curcumin is a polyphenolic ingredient with a lipophilic environment. The extraction of curcumin started from the root of turmeric rhizomes of a plant related to ginger origin, usually famous as Indian turmeric, which gives a typical yellow color[12]. Curcumin is a natural plant with many biological active uses for medicine[13], as an antioxidant[14], anti-tumor[15], hypoglycemic factor[16], and neuroprotective[17]. Zinc is implicated in all processes of an insulin-like organization, storage, and excretion. The direct activity of zinc in the body's metabolism depends on its enzymatic attraction and the way of a zinc-enzyme complex or metalloenzyme[18]. The deficiency of zinc leads to impairing the maturation of T and B cells and modifies cytokine secretion[19]. Zinc has done great work on the etiology of PCOS and other complications accompanied by this syndrome[20]. The study aims to describe the natural product of the plants that rises ovulation and diminishes the side effect of medications and to explain the role of zinc alone and when combined with curcumin.

Materials and Methods

Animals

Healthy female rats 12 weeks old, weighing (160-200) g, were used for the study. The rats were allowed to acclimatize for 3 weeks at the house of animals in the College of the Medicine/University of Basrah at control room temperature (22 ± 2 C °) at 12:12 hours (hr.) with a Light and dark cycle.

Drugs and Treatment

Curcumin supplement as curcumin 95% with piperine was bought from Aavalabs (Germany|) and curcumin standard from sigma (Aldrich), Metformin was acquired from (Merck - France), Zinc Sulphate (tablet) 125mg was gotten from MEGA (England), Letrozole and Carboxy Methyl Cellulose (CMC) were obtained from Sigma Aldrich (Germany).

Induction of PCOS

Induction of polycystic ovaries for female rats was done using Letrozole at a dose of 1 mg/ kg dissolved in 0.5 % Carboxy Methyl Cellulose (CMC) every day for 21 days. All female rats received Letrozole by gavage except the control groups received only CMC. The vaginal smears were examined daily to insure the regulation of the estrous cycle and were also measured by the microscopic presence of the predominant cell type

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for induction of PCOS after staining the smear in Giemsa stain[21].

Study Design and Treatment

The study included 56 virgin female rats randomly assigned into eight sub-groups each group contained 7 rats. Group one included 7 healthy female rats as the control group, while rest of 49 female rats suffering from PCOS induced by Letrozole were classified into seven groups as follows: PCOS -control group, PCOS-treated rats with 30 mg/kg zinc alone, PCOS-treated rats with 200 mg/kg curcumin standard, PCOS treated rats with 200 mg/kg curcumin supplement, PCOS treated rats with 200 mg/kg Curcumin standard plus 30 mg/kg zinc, PCOS treated rats with 200 mg/kg curcumin supplement plus 30 mg/kg zinc and PCOS treated rats with metformin at dose 50 mg/kg. After fourteen days of treatment, all female rats were slaughtered and blood was extracted from the inferior vena cava by sterile syringe then serum was separated by centrifugation at 3000 rpm for 15 minutes and stored at −20 Cº for biochemical analysis.

Bio-Chemical Parameters Estimation

Anti-mullerian hormone and insulin were determined by Immuno enzymatic assay, using ELISA Kit Monobindinc with the code number (2425-300) of AMH and (2425-300|) of insulin Kit. Glucose was measured by spectrophotometric kit liquiCHEK with the code number (11406001). HOMA-IR was measured as defined by Shen et. al. [22] as in Eq.1

$$HOMA - IR = \frac{Blood\ Glucose\ mg/dl \times Fasting\ Insulin\ \mu IU/ml}{405} \quad \ldots\ldots\ldots 1$$

Statistical Analysis

Biochemical measurements were analyzed by one-way ANOVA test and fisher Pairwise. Comparison tests and expressed by mean ±standard deviation. The statistical difference was tested for a level of probability at p≤ 0.05.

Results and Discussion

Table 1 shows the results of the effect of the therapeutic materials used in this study, as indicated by the treated groups described in the study design previously. Results revealed a significant p<0.05 increase in serum concentration of insulin and glucose in the PCOS control group (non-treated) (23.39±1.23) and (172.48±7.43) respectively when compared to their levels in the control group (12.69±0.72) and (87.31±5.02) respectively.

Moreover, after treating the PCOS groups with, zinc, Metformin, Cur standard, Cur. Standard +zinc, Cur. Suppl , and Cur .Suppl + zinc ,which recorded a significant decrease p<0.05 in serum concentration of insulin (20.05±0.49), (18.53±0.72), (15.63±0.72), (15.50±0.62), (14.48±0.42) and (13.39±0.99) respectively, and also significant decrease (p<0.05) in serum concentration of glucose (153.59±5.18), (110.83±4.21), (108.40±5.01), (100.24±3.38), (94.65±3.03) and (90.48±1.84) respectively in compared with PCOS control group.

Homeostatic model assessment for insulin resistance (HOMA-IR) results in Table 1 show a significant increase p<0.05 in the PCOS control group (9.97±0.77) when compared with the control group (2.73±0.260). After treatment with zinc, Metformin, Cur .Standard, Cur .Standard + zinc, Cur. Suppl, Cur. Suppl +zinc, a significant decrease p<0.05 occurred in HOMA-IR in all treated groups in comparison with PCOS control group. Cur .Suppl +zinc treated group showed a HOMA-IR level which did not differ from the control group.

In the current study, the serum of anti-mullerian hormone level showed a significant increase p<0.05 in the PCOS control group (8.901±0.77) when compared with the control group (3.66±0.33). The treatment of induced PCOS female rats with previous treatments revealed a significant decrease in AMH in all treated groups compared with the PCOS control group. The level of AMH in Cur. Suppl + zinc group showed the lowest level near control group.

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Table 1. Effect of zinc, Cur standard, Cur. Suppl. and metformin on serum insulin, glucose, HOMA-IR, and AMH levels in PCOS-induced female rats and healthy control.

Groups	Parameters			
	Insulin µIU/ml (mean ±SD)	Glucose mg/dl (mean ±SD)	HOMA-IR (Mean ±SD)	AMH ng/ml (mean ±SD)
Control	12.69 ±0.72 [f]	87.31 ±5.02 [f]	2.73 ±0.26 [f]	3.66 ±0.33 [f]
PCOS Control	23.39 ±1.23 [a]	172.48 ±7.43 [a]	9.97 ±0.77 [a]	8.90 ±0.77 [a]
zinc	20.05 ±0.49 [b]	153.59 ±5.18 [b]	7.60 ±0.18 [b]	7.77 ±0.76 [b]
Metformin	18.53 ±0.72 [c]	110.83 ±4.21 [c]	5.07 ±0.26 [c]	6.18 ±0.43 [c]
Cur. Standard.	15.63 ±0.72 [d]	108.40 ±5.01 [c]	4.18 ±0.24 [d]	5.15 ±0.50 [d]
Cur. Standard + zinc	15.50 ±0.62 [d]	100.24 ±3.38 [d]	3.80 ±0.20 [d]	5.52 ±0.46 [d]
Cur. Suppl.	14.48 ±0.42 [e]	94.65 ±3.03 [e]	3.38 ±0.08 [e]	5.08 ±0.42 [d]
Cur. Suppl. + zinc	13.39 ±0.99 [f]	90.48 ±1.84 [ef]	2.99 ±0.17 [f]	4.32 ±0.34 [e]
p-value	0.0014	0.0001	0.000015	0.00013

Values expressed in the small letters (**a, b, c, d, e**, and **f**) within a row represent mean significant differences at the $p<0.05$ level among the groups. Where the letter (**a**) explains the largest value. The different letters between the groups represent the significant differences ($p<0.05$), and similar letters show that there is non-significant difference between the groups $p \geq 0.05$.

Insulin resistance (IR) is the most common endocrine abnormality in females with the polycystic ovarian syndrome, the reason that the connection between inflammatory and insulin signaling pathways[23]. Insulin resistance may rise steroidogenesis with stimulation of the hypothalamus to flow Luteinizing Hormone (LH) in polycystic ovary syndrome by hyperinsulinemia [3]. The results of our study show elevated levels of insulin in induced rats which is in agreement with Shukrya and Muna results[24]. Hyperinsulinemia causes hyperandrogenism by inhibiting the hepatic synthesis of sex hormone-binding globulin. Likewise, higher insulin levels can fix insulin-like growth factor (IGF-1) receptors in the ovary, leading to elevated insulin-like growth factor and androgen production by theca cells [25].

In this study, the level of insulin and HOMA-IR decrease significantly in the PCOS group treated with zinc when compared with the PCOS control. The serum insulin and IR can decrease significantly by the administration of zinc 30 mg /kg only. Guler *et al.* have supposed that zinc insufficiency might play the main role in the pathogenesis of polycystic ovary, which may be linked with its long-term metabolic developments [26]. The significance of zinc has been reported in healthy subjects and diabetic patients because enters the synthesis and action of insulin [27]. Our result is in agreement with the study of Fazel et al who explained how zinc can improve PCOS [3]. The current results have proved that the types of treatments in our study could lower serum insulin concentration in PCOS female rats in all treated groups from its high serum concentration in non-treated PCOS female rats as presented in Table. 1. Furthermore, treatment with metformin reduces hyperinsulinemia and menstrual irregularity accompanied by a reduction of androgen levels in PCOS and also reduces inflammation, but it has a direct role in steroidogenesis [28]. Treatment with metformin raises insulin sensitivity, progresses ovulatory function, and improves lipid profile in PCOS [29]. Many studies found that the treatment with metformin improves PCOS through the significant decrease in serum insulin and positively improved sex hormone binding globulin (SHBG) [11]. In PCOS, it is well reported that metformin is beneficial in the decline of both insulin resistance and circulating androgens as well as in repairing ovulation[25]. Similar findings reported that metformin significantly decreased the serum insulin and IGF-I levels in PCOS. Metformin is the first choice in the treatment of PCOS and its metabolic disturbance[30]. Moreover, metformin affects both organs ovary and adrenal gland by decreasing androgen creation and decreasing pituitary luteinizing hormone, and elevating sex hormone binding globulin SHBG[31].

Metformin is helpful in PCOS by improving hyperinsulinemia by reducing insulin resistance but does not promote insulin secretion from B-cells [32].

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Several studies on metformin in PCOS were compiled in a meta-analysis, they demonstrated that metformin can stimulate ovulation, affects androgen creation for ovulation continuation. The direct role of metformin on the theca cells and that women with PCOS usually have insulin resistance and increased serum concentration of insulin and suffer dyslipidemia [33].

The serum levels of insulin and HOMA-IR in the PCOS-induced female rats significantly decreased after the treatment with curcumin standard and curcumin supplement in addition to the administration of their combination with zinc. This is due to curcumin stimulation of insulin release by enhancing the activity of beta cells of the pancreas to excretion of insulin [21]. Diamanti and Dunaif 2012 suggested that there is a post-binding defect in insulin receptor signaling in the ovary that affects metabolic in women with PCOS [34]. Curcumin has a significant role in PCOS by improving insulin resistance. In addition, the previous studies explained that the treatment with curcumin in PCOS -model rats significantly reduced the elevation in levels of blood glucose and HbA1c, which designates the helpful effect of curcumin in avoiding an increase in insulin resistance and diabetic complication [21].

Due to curcumin contains polyphenols and functions as an antioxidant, antibacterial, anti-inflammatory, anti-angiogenic, and antimutagenic via scavenger of reactive oxygen species [35-38], the effects of treatments with curcumin standard and curcumin supplement were superior to those with metformin. According to studies, curcumin may be a potent antioxidant that reduces the impact of oxidative stress by acting in concert with many molecular processes. It reduces the amount of oxidative stress, which is related to the ability to chelate heavy metals or normalize the activity of several enzymes, among other things. A significant mechanism of curcumin to regulate inflammation is that it powerfully decreased ROS-producing enzymes [39].

In addition, the Food and Drug Administration (FDA) stipulated that curcumin is a chemical that is generally regarded as healthful [12]. Alizadeh and Khayuri have published a systematic review and meta-analysis describing the effect of piperine on the bioavailability of curcumin and on boosting its antioxidant potential [40]. In the current study, the PCOS group had a higher glucose level when compared with the control group, this result is similar to the previous results[41].

Alternatively, our results described a reduction in the glucose levels, in all treated groups, and show that supplementation of zinc significantly reduced the glucose level when compared with the PCOS control group. The role of zinc as a trigger activates key signaling molecules elaborate in glucose homeostasis and can provide circumstances to use this ion medicinally in treating disorders connected with dysfunctional zinc signaling[42].

Anti – Mullerian hormone (AMH), was defined for the first time in 1947 by the scientist Alfred Jost. It is formed by the Sertoli cell in the testis and it takes a role through embryogenesis by reducing the improvement of Mullerian duct in men embryos so, it plays a role in male sex characteristic[43]. Elevated concentration of AMH may cooperate with the pathophysiology of PCOS [44]. In addition, recent studies have explained the association between AMH and insulin resistance and have discovered that AMH and insulin influence the generation of steroids and folliculogenesis [45].

The level of AMH in our experiment showed an elevation in PCOS models, which was following former studies of elevated AMH in PCOS [46]. The results of Ran, et al agree with our result which shows AMH level is two to double times higher than healthy in women with PCOS and has good sensitivity and specificity for the diagnosis of PCOS as well as the follow-up and prognosis. Thus, higher AMH levels in patients with PCOS are a consequence of elevated production by developing antral follicles in the polycystic ovaries. Likewise, AMH's role in follicular development suggests its probable value as a marker for the category and degree of ovarian dysfunction in women with polycystic ovary syndrome (PCOS) [47]. The results of AMH in PCOS treated with zinc decrease significantly when compared with PCOS control. The previous study has shown that zinc inter in the role of ovulation[48]. The effect of treatment with metformin on PCOS rats was explained by reducing AMH significantly. Some studies concerning women with PCOS have tried to explore the AMH level in serum during treatment with metformin. They found a significant decrease in AMH after 8 months of metformin administration in PCOS women[49].In our study, the treatment of PCOS rats group with curcumin standard, curcumin

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supplement, and their combination with zinc could decrease serum AMH levels significantly, but curcumin supplement plus zinc has a greater reducing effect than other treatments. This is related to the fact that curcumin has many different effects on PCOS. Our findings revealed that curcumin might be a safe and beneficial complement to ameliorate PCOS-related hyperandrogenemia and hyperglycemia which are in agreement with Heshmati results[50].

Conclusion

This study showed the potency of curcumin in both types (standard curcumin and curcumin supplement) in reducing the elevated levels of insulin, AMH, glucose, and HOMA-IR in induced PCOS rats. Better reductions can be obtained when using a curcumin supplement with zinc. Our study introduces curcumin in combination with zinc as a safe and effective alternative treatment to traditional medical prescriptions for PCOS.

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Author's Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given the permission for re-publication attached with the manuscript.
- The authors signed an animal welfare statement.
- Authors signed ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee in University of Basrah.
- Ethical approval: The study was approved by the Department of Chemistry in the College of Science, University of Basra. According to the ethical approval issued by the College of Pharmacy, University of Basra (Approval Number EC11 in 5 / 12/ 2021).

Author's Contribution Statement

S. M. A., S.A. Z. and I. J. A. contributed to the design of the research, analysis of the results and to the writing of the manuscript. S. M. A contributed to determine biochemical parameters in research. All authors discussed the results and commented on the manuscript

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دراسة تأثير الكركمين(قياسي و مكمل غذائي) والزنك على تراكيز الكلوكوز، الانسولين، مقاومة الانسولين وهرمون مضاد لمولر في نموذج الجرذان المصابة بتكيس المبايض المستحدث

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الخلاصة

الغرض من الدراسة الحالية للتحقق من تأثير الكركمين بشكليه (مكمل غذائي، قياسي) ، والزنك ، ثم استخدامهما معًا لإظهار تأثيرهما على مستويات الجلوكوز، الأنسولين، مقاومة الانسولين، والهرمون المضاد للمولر (AMH) في نموذج إناث الفئران المصابة بمتلازمة تكيس المبايض الناتجة عن تجريع الجرذان 1 ملغ / كجم / يوم من البتروزول لمدة 21 يومًا تليها فترة علاج مدتها 14 يومًا من علاجات مختلفه شملت الزنك 30 مجم / كجم ، والكركمين القياسي 200 مجم / كجم ، ومكمل الكركمين 200 مجم / كجم ، (الكركمين القياسي مع الزنك) ، (مكمل الكركمين مع الزنك) و الميتفورمين كعلاج معتمد. بعد العلاج ، تم قتل جميع إناث الجرذان ، وجمعت عينات الدم من الوريد الأجوف السفلي لكل الجرذان للقياسات البيوكيميائية. تم قياس تراكيز الأنسولين و AMH باستخدام تقنية الاليزا ELISA. تم تحديد مستوى الجلوكوز باستخدام طريقة الطيفيه بينما تم قياس مقاومة الأنسولين حسابيا. أظهرت النتائج أن إعطاء الليتروزول كمثبط للأروماتاز أدى إلى ارتفاع كبير في الهرمون المضاد للمولر (AMH) ، الجلوكوز، الأنسولين، ومقاومة الأنسولين في النموذج المصمم لمتلازمة تكيس المبايض. اظهر الكركمين (القياسي و المكمل الغذائي) والزنك انخفاضًا معنويًا في مستويات الأنسولين في جميع مجموعات العلاج ، بينما كان التأثير أكثر وضوحًا عند تناول الزنك مع مكمل الكركمين.كما أظهرت النتائج أيضًا انخفاضًا معنويًا في الجلوكوز ومقاومة الانسولين، مما يدل على قدرة مكمل الكركمين والزنك على استعادة الجلوكوز و مقاومة الانسولين إلى مستواهما الطبيعي في مجموعة التحكم الصحية. انخفض هرمون مضاد مولر(AMH) بشكل معنوي لجميع المجموعات التي تناولت الكركمين بكلا الشكلين و الكركمين والزنك معًا ، بينما كان الانخفاض معنويًا للغاية في مكملات الكركمين والزنك.

الكلمات المفتاحية: هرمون مضاد مول (AMH)، الكركمين(Cur)، مقاومة الانسولين (IR)، متلازمة تكيس المبايض (PCOS)، زنك.