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Synergistic Power of Allicin and Lycopene: Transforming Behavioral Outcomens in Polycystic Ovarian Syndrome

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ABSTRACT

Reproductive, metabolic, and psychological disturbances are observed in polycystic ovarian syndrome (PCOS), psychological disturbances include depression, anxiety, stress, and reduced quality of life. Obesity was found to be the major factor causing depression and emotional stress among patients with PCOS. Letrozole (LET) effectively creates PCOS and it shows little depression and anxiety. In the present study induction of depression and anxiety was studied by using a combination of a high-fat diet (HFD) and LET (PCOS control group), followed by its treatment with allicin, lycopene, and their combination. The combination of HFD and LET resulted in complete acyclicity in rats along with hyperandrogenism, significant depression was seen in the open field test and forced swim test in the PCOS control group along with anxiety which was observed through the elevated plus-maze test and hole board test, treatment with allicin, lycopene and their combination restored the estrous cyclicity and hormone levels, followed by the positive effect on behavioral tests, combination of allicin and lycopene has shown a synergistic effect behavioral parameters of PCOS. Thus, the HFD+LET can be a good animal model to study psychological changes in PCOS, a combination of allicin and lycopene can be a good treatment option for PCOS and its related psychological condition.

Keywords: High-fat diet, Letrozole, Polycystic ovarian syndrome, Allicin, Lycopene, Depression, Anxiety.

1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrine disorder among women of reproductive age wherein ovaries may develop fluid-filled follicles (cysts).[1,2] Cysts in the body induce a variety of metabolic, reproductive, and psychological disturbances.[3] Reproductive changes include androgen excess, which causes hirsutism and acne, as well as oligo- or anovulation and infertility.[4] Depression, anxiety, reduced quality of life, and a variety of stress responses are all examples of psychological disturbances associated with PCOS.[5] Much research has previously demonstrated that anxiety and depression are more common in women with PCOS than in healthy women, with most of these studies focusing on depression, but a study by Mansson et al. has found that anxiety in PCOS is also an important issue.[5,6]

PCOS and obesity (BMI ≥ 30 kg/m^2) have a well-established link. Women with PCOS are more prone to develop abdominal or visceral obesity, particularly leading to negative metabolic outcomes such as insulin resistance.[7] Obesity was pointed out to be the major factor causing depression and emotional stress among patients with PCOS.[8]

Estradiol valerate (EV), dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), and letrozole (LET) induced models have all been examined as experimental models for PCOS.[9] Even though these models offer useful insights into the pathogenic mechanisms of PCOS and therefore can assist in the improvement of PCOS therapies, their contribution to PCOS-induced anxiety and depression has received little attention.

We have previously published a part of this work which was conducted at the same time using LET and HFD which caused obesity and has shown metabolic and ovarian aberrations, but in this paper, we present depression and anxiety-like behavior in the LET+HFD model, and the treatment of behavioral parameters with allicin, lycopene and their combination.[10]

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Allicin, an organosulfur compound found in garlic has been utilized to treat various ailments since ancient times.[11] It possesses antioxidant, anti-inflammatory, antidiabetic, and antidepressant activity.[12-15]

Lycopene is considered to be one of the most important antioxidants that can contribute to reducing or preventing the psychological damage that leads to infertility.[16,17] It also possesses anti-inflammatory and anti-diabetic properties.[18,19]

Therefore, the present study aims to develop an animal model for PCOS-induced depression and anxiety and to study its treatment by using allicin and lycopene and combination.

2. MATERIAL AND METHODS

2.1. Experimental animals

We utilized 36 virgin female Wistar rats of approximately 150-200 g weight. The animals were obtained from GENTOX Bio Services Pvt. Ltd. Hyderabad, India, and then were put in the institution's animal housing area for a week to acclimate. All the animals were kept in regular polypropylene enclosures in a controlled environment at a temperature of 20-22°C, a humidity of 55 ± 5%, and a 12-hour light/dark cycle. Following protocol code GPRCP/IAEC/23/19/02/PCL/AE-6B-rats-F-36, the investigation was authorized by the Institutional Animal Ethics Committee (IAEC) and carried out as per the criteria of the committee for the purpose of control and supervision of experiments on animals (CPCSEA).

2.2. Drugs and chemicals

Allicin 5% was procured from Vijay Herbal Products, (New Delhi, India), Lycopene 10% was obtained from (SV Agrofood Mumbai, India), Metformin 500 mg (Obimet) was obtained from Corona Remedies Pvt. Ltd. (Ahmedabad, India). HFD ingredients were obtained from Behlawa Enterprises (Mumbai, India), and choline bitartrate was procured from Universe Industries (Maharashtra, India). LET (Letero) was purchased from Hetero Health Care Pvt. Ltd, crystal violet was purchased from S.D. Fine Chemicals, methanol, and saline were obtained from local sources. TNF-α kit was purchased from Infobio, Delhi, India.[20]

Control and HFD diets were reported in the previously published paper of this study.[20]

2.3. Induction of PCOS

The study duration was 12 weeks, animals were divided into the control group receiving the control diet (10% energy from fat), the PCOS control group, which received LET (0.5 mg/kg p.o.), and HFD (45% energy from fat) for 6 weeks (Begum N et al., 2022). After 6 weeks of induction PCOS induced rats were divided into five groups containing six rats each, PCOS induced group, the Allicin group received 320 mg/kg allicin p.o., the Lycopene group received 160 mg/kg lycopene p.o., the combination group received a combination of allicin 160 mg/kg p.o and lycopene 80 mg/kg p.o., and metformin group received 100 mg/kg metformin p.o., all groups were continued on HFD for next 6 weeks. 1% carboxymethylcellulose was used as a vehicle.

Vaginal smears were collected daily and evaluated microscopically using crystal violet staining to confirm PCOS induction.[10] Irregular estrous cyclicity and elevated testosterone levels were the main criteria for selecting PCOS rats; during the study period body weight was recorded at weekly intervals.[20]

2.4. Estimation of testosterone levels

Testosterone levels were estimated using a TSTO kit by ADVIA Centaur, during week 12.

2.5. Behavioral estimations

All behavioral estimations were done during weeks 11 and 12 of the study.

2.5.1. Evaluation of anti-depression potential

2.5.1.1. Open field test

A wooden cage (44 cm length x 44 cm width base, 44 cm high walls) was used as the locomotor activity apparatus. The floor was divided into 16 squares (each measuring 11 cm by 11 cm). A 5-minute locomotor activity test was performed and recorded on each rat.

The rats were carefully placed in one of the cage's corners at the start of the experiment, and the following variables were measured (a) Number of squares crossed (crossings; when the rat crossed from one square to another with its rear legs), (b) Time spent rearing (when the rat assumed a vertical posture relative to the cage floor), and (c) Time spent grooming (paw licking, nose/face grooming, head washing, body grooming/scratching, leg licking, and tail/genital grooming). The time spent in the center and corners of the locomotor activity cage was also measured.[21]

2.5.1.2. Forced swim test

We selected a circular plastic pool (30 cm x 50 cm) filled to a depth of 25 cm with water (25°C ± 1°C). The degree of immobility was recorded. The total time of immobility was measured by two independent observers. The rats were trained to swim one day before the forced swim test for 15 minutes. The test was performed on the next day of the training, this model is made up of a single 6-minute experiment. During the last 4 minutes of the session, immobility time was observed and recorded.

When the rat floated without making strong movements that caused water displacements and just kept its head above the water surface for more than 2 seconds, it was considered immobile.[21]

2.5.2. *Evaluation of anxiolytic potential*

2.5.2.1. *Hole board test*

Higher anxiety has long been recognized to impair rats' typical exploratory behavior, which may be measured using the hole board test. The hole board test includes putting the rat in the center point of wooden cardboard (44 cm × 44 cm) with 16 evenly placed holes and recording the number of head dips for 5 minutes to assess guided explorations by rats. The decrease in the number of head dips suggested a decrease in exploratory behavior and therefore increased anxiety.[22]

2.5.2.2. *Elevated plus-maze test*

The apparatus is made of wood and includes two open and closed arms that were elevated 50 cm above the floor. The open arms measured 50 cm in length and 10 cm in width. The closed arms measured 50 cm in length, 10 cm in breadth, and 50 cm in height. A camera was mounted above the equipment to observe the rats' behavior. Later two independent observers measured the behavioral parameters until a 95% agreement was reached.

The rats were placed in the elevated plus-maze in the center, facing an open arm, and the movements were recorded for 5 mins. The following variables were evaluated: (a) Time spent on the open arms, (b) Number of entries into the open arms, (c) Number of entries into the closed arms, (d) Total number of entries into the open and closed arms, (e) Percentage of open arm entries ([open arm entries] / [total arm entries] × 100), and (f) The anxiety index.[21]

The anxiety index (AI) was calculated according to the formula.

AI = 1 – [(time spent on the open arms/test duration) + (entries into the open arms/total number of entries)/2].

To minimize abrupt behavioral changes produced by sensory stimuli (i.e., volatile chemicals) present in the urine of the previous rat, the elevated plus-maze, hole board apparatus, and locomotor activity cages were meticulously disinfected with a 15 percent ethanol solution after every testing session, in the forced swim test the water in the pool was changed with every test.

2.5.3. *Assay of TNF-a*

For assessment of TNF-α level hippocampal slices were homogenized in PBS. Homogenates were centrifuged at 14000 g for 30 min and supernatant was retained. Protein concentration was measured using the Lowry's method. TNF-α was measured by enzyme-linked immunosorbent assay (ELISA TNF-α kit) according to the manufacturer's instructions. The final concentrations were then adjusted for the protein content in the sample.[23]

2.5.4. *Statistical Analysis*

Data values are expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test using GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA) to compare more than two groups. Differences were considered statistically significant when $P < 0.05$.

3. RESULTS

3.1. Effect of allicin, lycopene, and their combination on body weight

An increase in body weight was observed in the PCOS control group during the last 6 weeks of the study when compared to the control group ($P < 0.001$).[20] Treatment with allicin caused a decrease in body weight from the 9th week onwards ($P < 0.001$), which was restored to normal levels by the 11th week. Treatment with lycopene caused a decrease in body weight from the 7th week onwards ($P < 0.01$), and these levels were restored to normal by the 10th week. The combination group has shown a decrease in body weight from the 8th week ($P < 0.01$) when compared to the PCOS control group, which was restored to normal by the 10th week (Fig. 1).

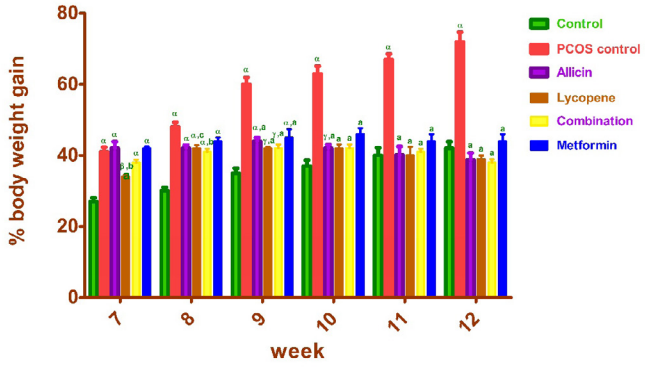

Figure 1: Effect of allicin, lycopene, and their combination on body weight

Data are expressed as mean ± SEM (n=6) and analyzed by ANOVA followed by Tukey's post hoc test for comparison of means. $^{\alpha}P < 0.001$, $^{\beta}P < 0.01$, and $^{\gamma}P < 0.05$, when compared with the control group; $^{a}P < 0.001$, $^{b}P < 0.01$, and $^{c}P < 0.05$ when compared with the PCOS control group. PCOS, polycystic ovary syndrome.

The vaginal smear of the PCOS group demonstrated the dominant cells i.e., leucocytes in the diestrous phase/ persistent cornification in the oestrous phase, showing complete acyclicity. As the study progressed, persistent cornification gradually increased in the PCOS group when compared to the control group.[20] Treatment with allicin, lycopene, combination, and metformin gradually induced cyclicity in the PCOS-induced rats.

3.2. Effect of allicin, lycopene, and their combination on testosterone levels

An increase in testosterone level was observed in the PCOS control when compared with the control group ($P < 0.001$).[20] Treatment with allicin, lycopene, combination, and the standard drug metformin caused a decrease in the levels of testosterone and further restored it to normal levels ($P < 0.001$) (Fig.2).

3.3. Forced swim test

The immobility time was increased in the PCOS control group when compared with control group ($P < 0.001$), treatment with allicin, lycopene, combination, and metformin caused decrease in immobility time ($P < 0.001$), when compared with PCOS control group, and restored it to normal levels, also treatment with combination of allicin and lycopene caused further decrease in immobility time when compared with control group ($P < 0.01$), thus indicating synergistic potential of the combination fig.3.

3.4. Hole board test

A decrease in the number of head dips was observed in the PCOS control group when compared with the control group ($P < 0.001$), whereas treatment with allicin, lycopene, combination, and metformin showed an increase in number of head dips ($P < 0.001$), when compared with PCOS control group, treatment with lycopene and combination has shown further significant increase in number of head dips when compared with control group ($P < 0.05$ and $P < 0.001$), showing a good response of lycopene and synergistic potential of the combination of the drugs (Fig. 4).

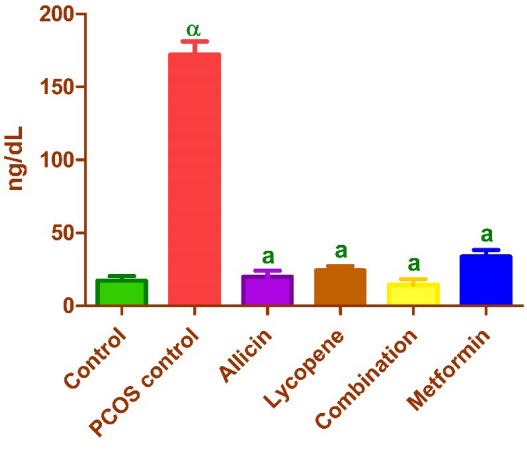

Figure 2: Effect of allicin, lycopene, and their combination on testosterone levels.

Data are expressed as mean ± SEM (n=6) and analysed by ANOVA followed by Tukey's post hoc test for comparison of means. $^{\alpha}P < 0.001$, when compared with the control group; $^{a}P < 0.001$, when compared with the PCOS control group. PCOS, polycystic ovary syndrome.

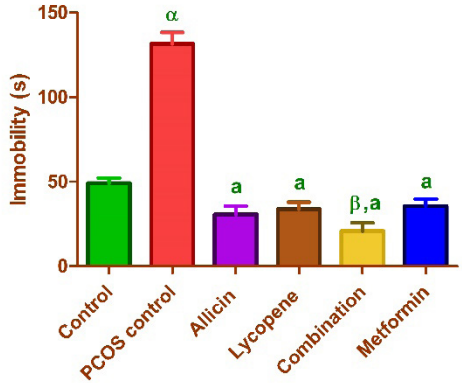

Figure 3: Estimation of immobility time

Data are expressed as mean ± SEM (n = 6) and analyzed by ANOVA, followed by Tukey's post hoc test for comparison of means. $^{\alpha}P < 0.001$, $^{\beta}P < 0.01$, when compared with the control group. $^{a}P < 0.001$, when compared with the PCOS control group. PCOS, polycystic ovary syndrome.

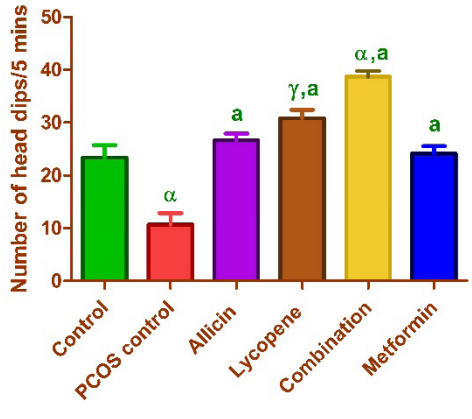

Figure 4: Number of head-dips (Hole board test)

Data are expressed as mean ± SEM (n = 6) and analyzed by ANOVA, followed by Tukey's post hoc test for comparison of means. $^{\alpha}P < 0.001$ and $^{\gamma}P < 0.05$, when compared with the control group. $^{a}P < 0.001$, when compared with the PCOS control group. PCOS, polycystic ovary syndrome..

3.5. Elevated plus-maze parameters

Time spent on the open arm was decreased in the PCOS control group ($P < 0.001$) when compared with the control group; an increase in the time spent on the open arm was observed in the allicin, lycopene, combination, and metformin group ($P < 0.001$) when compared to PCOS control group, and this was restored to normal in the combination group.

The number of entries into the open arm was decreased in the PCOS control group when compared with the control group ($P < 0.001$), and an increase in the number of entries was observed in the allicin, lycopene, combination, and metformin group ($P < 0.001$) when compared with PCOS control group, and it was restored to normal.

The number of closed-arm entries was reduced in the PCOS control group ($P < 0.001$) when compared to the control group. Treatment with allicin, lycopene, combination, and metformin increased the number of closed-arm entries ($P < 0.001$, $P < 0.001$, $P < 0.01$, and $P < 0.001$), and restored levels to normal.

The percentage of open-arm entries was reduced in the PCOS control group ($P < 0.001$) when compared to the control group. Treatment with allicin, lycopene, combination, and metformin increased the percentage of open arm entries ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P < 0.01$), this was restored to normal in allicin, lycopene, and combination group.

The anxiety index was increased in the PCOS control group ($P < 0.001$) when compared to the control group. Treatment with allicin, lycopene, combination, and metformin decreased the anxiety index ($P < 0.001$) when compared to the PCOS control group, and this was reduced to normal levels in the combination group.

The results of elevated plus-maze parameters are shown in Table 1.

3.6. Open field test parameters

The number of crossings was reduced in the PCOS control group when compared with the control group ($P < 0.001$), treatment with allicin, lycopene, combination, and metformin increased the number of crossings ($P < 0.001$), when compared to the PCOS control group, and it was restored to normal.

The time spent in grooming was decreased in the PCOS control group ($P < 0.001$) when compared to the control group, treatment with allicin, lycopene, their combination, and metformin increased the time spent in grooming ($P < 0.001$), and it was restored to normal in allicin, lycopene, and combination groups.

The time spent in rearing was decreased in the PCOS control group ($P < 0.001$) when compared to the control group, treatment with allicin, lycopene, their combination, and metformin increased the time spent in grooming ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.05$), and it was restored to normal in allicin, lycopene, and combination groups.

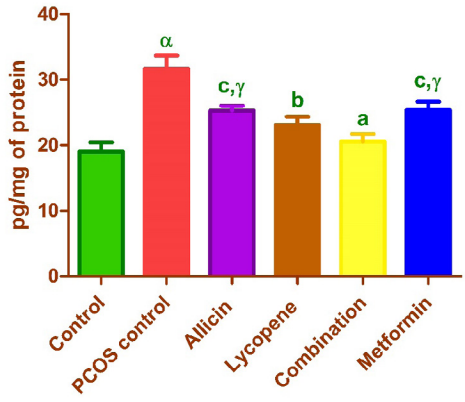

Figure 5: Effect of allicin, lycopene, and their combination on Brain TNF-alpha levels

Data are expressed as mean ± standard error of the mean (SEM) (n = 6) and analyzed by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for comparison of means. $^{\alpha}P < 0.001$ and $^{\gamma}P < 0.05$, when compared with the control group. $^{a}P < 0.001$, $^{b}P < 0.01$, and $^{c}P < 0.05$ when compared with the PCOS control group.

Table 1: Parameters of the elevated plus maze (EPM).

Parameter	*Control*	*PCOS control*	*Allicin*	*Lycopene*	*Combination*	*Metformin*
Time spent on the open arm (s)	102±3.2	$11±3.3^{\alpha}$	$59±2.6^{\alpha,a}$	$73±3.3^{\alpha,a}$	$113±2.8^{a}$	$63±3.8^{\alpha,a}$
Number of entries into the open arm (n)	7.7±0.49	$1.7±0.21^{\alpha}$	$6.3±0.49^{a}$	$7.0±0.37^{a}$	$8.0±0.45^{a}$	$5.5±0.43^{\gamma,a}$
Entries into the closed arm (n)	13±0.72	$7.5±0.76^{\alpha}$	$13±0.92^{a}$	$14±0.49^{a}$	$12±0.43^{b}$	$13±0.89^{a}$
Total entries in the arms (n)	20±1.1	$9.0±1.1^{\alpha}$	$19±0.68^{a}$	$21±0.76^{a}$	$20±0.56^{b}$	$18±0.77^{a}$
Percentage of entries into the open arm (%)	36±1.1	$18±1.2^{\alpha}$	$34±3.3^{a}$	$34±0.96^{a}$	$41±1.7^{a}$	$31±2.7^{b}$
Anxiety Index	0.64±0.010	$0.87±0.025^{\alpha}$	$0.73±0.014^{ß,a}$	$0.71±0.0086^{\gamma,a}$	$0.61±0.0091^{a}$	$0.74±0.013^{\alpha,a}$

Data are expressed as mean ± SEM (n = 6) and analyzed by ANOVA, followed by Tukey's post hoc test for comparison of means. $^{\alpha}P < 0.001$, $^{\beta}P < 0.01$, and $^{\gamma}P < 0.05$, when compared with the control group. $^{a}P < 0.001$ and $^{b}P < 0.01$ when compared with the PCOS control group. PCOS, polycystic ovary syndrome.

Table 2: Parameters of open field test (OFT).

Group	Crossing (n)	Grooming (s)	Rearing (s)	Periphery (s)	Center (s)
Control	64±2.9	47±2.5	62±2.0	245±3.3	55±3.3
PCOS control	37±2.0$^{\alpha}$	16±1.5$^{\alpha}$	27±1.8$^{\alpha}$	287±1.5$^{\alpha}$	14±1.5$^{\alpha}$
Allicin	64±2.4^{a}	39±1.9^{a}	52±2.5^{a}	256±3.3^{a}	44±3.3^{a}
Lycopene	64±3.4^{a}	42±2.4^{a}	57±2.2^{a}	260±7.2^{a}	47±3.5^{a}
Combination	75±2.8^{a}	50±2.8^{a}	63±2.4^{a}	249±3.4^{a}	52±3.4^{a}
Metformin	60±2.5^{a}	37±2.2$^{\gamma,a}$	38±3.2$^{\alpha,c}$	263±2.7$^{\gamma,b}$	37±2.7$^{\beta,a}$

Data were expressed as mean ± SEM (n=6) and analyzed by ANOVA followed by Tukey's post hoc for the comparison of means. $^{\alpha}P<0.001$, when compared to the control group, $^{a}P<0.001$, when compared to the PCOS control group.

Time spent in the periphery of the open field was increased in the PCOS control group ($P < 0.001$) when compared to the control group, treatment with allicin, lycopene, their combination, and metformin decreased the time spent in the periphery ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.01$), and it was restored to normal in allicin, lycopene, and combination group).

Time spent in the center of the open field was decreased in the PCOS control group ($P < 0.001$) when compared to the control group. Treatment with allicin, lycopene, their combination, and metformin increased the time spent in the center of the open field, ($P < 0.001$), this was restored to normal in allicin, lycopene, and combination groups.

The results of open field parameters are shown in Table 2.

3.7. Brain TNF-α levels

The levels of TNF-α were increased in the PCOS control group ($P < 0.001$) when compared to the control group. Treatment with allicin, lycopene, their combination, and metformin decreased the levels of TNF-α ($P < 0.05$, $P < 0.01$, $P < 0.001$, $P < 0.05$), and the levels were restored to normal in the combination group (Fig. 5).

4. DISCUSSION

High levels of depression and anxiety have been observed in patients with PCOS because of varied reasons such as high body mass index (BMI), increased androgen levels, menstrual disturbances, infertility, hirsutism, and acne, thus, international, and Indian guidelines suggest that all women with PCOS should be considered for psychological factors.[5,8] In animal studies, Ressler et al. have found that anxiety-related behavior was greater in DHT-treated animals and suggested a link between hyperandrogenism and anxiety, whereas the addition of HFD has shown greater depressive-like behavior. In DHEA+HFD-induced models of PCOS, slight depression-like behavior was observed, which was also seen in the DHEA group, thus, DHEA-treated mice show a depressive predisposition, regardless of the diet.[7,24]

In the present study, the PCOS control group demonstrated complete acyclicity of the estrous cycle along with hyperandrogenism which can be because of the androgenic effect of LET by inhibiting the aromatase enzyme, and hyperinsulinemic IR and glucose intolerance of HFD.[25,26] Mohammadi et al. found that LET-induced rat models acquired severe depression, minor anxiety-like behaviors, and impaired memory compared to control animals, similar results were observed in the present study.[24,27] In both, the hole board test and elevated plus maze test PCOS control group has shown significant depressive and anxiety effect, this can be because of presence of high-fat content in their feed, which leads to obesity, which is mainly linked with PCOS induced depressive and anxiety symptoms.[20,24]

TNF-alpha is identified as an important key pro-inflammatory cytokine in the pathophysiology of depression and anxiety.[28,29] Spagnuolo et al, have shown that high fat diet fed rats have shown increased brain TNF-alpha levels.[30] Similarly, in the present study, TNF-alpha levels were significantly increased in PCOS control groups.

It was previously shown that Welsh onion root restores the ovarian function in letrozole induced polycystic syndrome, but the effect of allicin in PCOS has never been studied before, present study showed that allicin possesses anti-hyperandrogenic property and can restore the cyclicity in PCOS induced rats, also as garlic extract possess anti-depressive activity, in present study allicin has shown anti-depressive and anxiolytic property.[15,31] Effect of lycopene on PCOS-induced rats was not studied before, in present study we found that lycopene possesses antihyperandrogenic property and has shown anti-depressive and anxiolytic effect, its anti-depressive and anxiolytic effect was previously studied by Kumar et al.[32]

Synergistic anti-oxidant effect of lycopene with garlic have been reported earlier, similar to this we have

observed synergistic activity of lycopene with allicin, on ovarian and behavioral parameters of PCOS.[33]

5. CONCLUSION

HFD+LET can be a good animal model to study psychological changes in PCOS, both allicin and lycopene has shown positive response on behavioral parameters of PCOS, and their combination act synergistically to show better response than the individual drugs, thus, they can be a good treatment option for PCOS and its related psychological condition.

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