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# Effect of Turmeric Extract on Serum Adiponectin Levels, Esteroid Hormone Profiles and Sexual Function in Stressed Women: A Randomized Triple-Blind Clinical Trial

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**ABSTRACT**

**Background & aim:** Sexual dysfunction will result from chronic stress, which negatively affect sexual activity and the secretion of estrogen and progesterone. Additionally, adiponectin that increases steroid hormones release could be influenced by different plants including turmeric . Thus, this study examined the effect of turmeric extracts on serum adiponectin level, steroid hormone profiles and sexual function in stressed women.

**Methods**: In this randomized triple-blind clinical trial, 57 women with moderate to severe stress and poor sexual function visited the gynecology clinic of a teaching hospital affiliated with Iran University of Medical Sciences, Tehran, Iran from April to August 2020. Participants were selected by convenience method and then were randomly assigned to the intervention and control groups. The intervention group received 300 mg of turmeric extract daily for four weeks, while the control group used a placebo containing 500 mg of starch. Tools used included the demographic questionnaire, the Depression Anxiety Stress Scale (DASS) and the Female Sexual Function Index (FSFI). Adiponectin, estradiol, progesterone, steress and sexual function were measured in all participants before and four weeks after the intervention. Data analyzed by SPSS (version 14).

**Results:** Results showed a significant difference between the two groups in terms of post-intervention adiponectin (P<0.001), estradiol (P=0.006), and progesterone (P<0.001). Also, post-intervention sexual function score was significantly different between the two groups (P<0.001).

**Conclusion:** Turmeric can enhance estradiol hormone profiling and as a consequence sexual function of women. Healthcare providers can recommend consuming turmeric-containing foods to women for improvement of their sexual function.

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## Introduction

Sexual function is critical to the survival of human biengs. Sexual function is used by organisms for pleasure and increased communication with the opposite sex (1).

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According to the World Health Organization, one of the most important aspects of health to consider is sexual health. To improve sexual function, sexual health services should be provided at the primary level of care. Sexual dysfunction is caused by chronic stress (2). Studies have shown the negative effect of stress on sexual activity (3). Stress also negatively affects reproduction; mental and physical stress both reduce sexual function. Many women who have experienced stress have sexual dysfunction in terms of sexual motivation and orgasm (4). Estradiol and progesterone are hormones that boost female libido (5-6); adiponectin stimulates progesterone and estradiol secretion (7-8) and adiponectin can cross the blood-brain barrier. The behavior of adipose tissue and adiponectin secretion under stress have been investigated in previous studies. The activator peroxisome proliferator-activated receptor gamma (PPAR) belongs to the nuclear receptor family and has two isoforms of PPARγ and 2 PPARγ, the first of which is abundant in adipose tissue but also found in other tissues like ovary and other Reproductive organs , and the second of which is only found in adipose tissue. In fact, PPARγplays an important role in adiponectin expression. (9, 10). Studies have shown that some foods can potentially increase serum adiponectin levels (11,12). Adiponectin gene expression was also increased in mice after consuming turmeric and jujube (11, 12). Curcumin and turmeric, on the other hand, have received FDA (food and drug administration) approval and have been used in previous studies (13). Several studies have shown that this spice is widely consumed and important in the health, food, and cosmetic industries (14). Therefore, this study aimed to investigate the effect of turmeric on serum adiponectin level, steroid hormone profiles and sexual function in stressed women.

## Materials and Methods

This study was a randomized triple-blind clinical trial. This is the phase 2 clinical trial that was carried out from April to August 2020. It was registered with code of IRCT20190219042768N1 in IRCT (Iranian Registry of Clinical Trials).

The participants were selected through convenience sampling from women aged 19 to 45 years who visited the gynecology clinic of a teaching hospital affiliated with Iran University of Medical Sciences, Tehran, Iran and then were randomly assigned to the intervention and control groups . The inclusion criteria were as follows: Farsi-speaking Iranian women, being married, not being in the pregnancy or breastfeeding period, not being infertile, not having any history of medical problems such as diabetes and hypertension, non-affliction with psychological diseases, infections, pelvic pathology, and other medical problems, not taking hormonal or contraceptive drugs, not having exposure to the stressful situations such as the death of relatives over the last three months, not taking drugs that interfere with sexual function (e.g. cyproterone acetate), and not being on special diets such as vegetarianism. The exclusion criteria were also as follows: developing a medical problem during the study, unwillingness to continue the research, and failure to use the desired extract correctly.

A pilot study was done to determine the sample size. Assuming α=0.05, β=0.2, a confidence level of 95%, a test power of 80%, and an attrition rate of 10%, the sample size was determined to be 30 in each group.

$$n = \frac{2\sigma^2 \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{(\mu_1 - \mu_2)^2}$$

$$\sigma^2 = \frac{S_1^2 + S_2^2}{2}$$

This study employed a three-part instrument for data collection. The first part of the instrument included a demographic questionnaire with seven items about age, weight, height, BMI, marital age, marital duration, and educational level. Female Sexual Function Index (FSFI) used to measure women's sexual function with 19 items in 6 independent domains: desire, psychological stimulation, moisture, orgasm, satisfaction, and sexual pain. The FSFI score is the sum of the scores received in all five domains. The maximum possible score on this scale is 36, and a score of 28 or less in Iran and a score of 26.5 or less in other countries indicate sexual disorders (15).

In a study by Mohammadi et al (2015), the reliability of the scale was calculated by analyzing the stability or internal consistency coefficient of the questions, Cronbach's alpha was 0.70 and above in all subjects for each of the domains and the whole scale. Also, they reported the reliability of the whole scale as 0.88 and for subscales from 0.79 to 0.86 (15). Depression Anxiety Stress Scale (DASS) is a set of three self-report scales for depression, anxiety, and stress. This scale is used to assess the severity of the primary symptoms of depression, anxiety, and stress. A person must specify the status of a symptom during the week in order to complete the questionnaire. Each subscale comprises seven items, and the total score is calculated by adding the scores of the questions in that category. Each item is scored based on a 4-point Likert scale from 0 to 3. Only the stress subscale was used in this study. The validity and reliability of this questionnaire in Iran have been investigated by Samani and Jokar et al (2016). The statistical method of confirmatory factor analysis using the principal components method has been used for the validity of this scale. Cronbach alpha for depression, anxiety, and stress was 0.81, 0.74, and 0.78 respectively (16).

After obtaining informed consent and explaining the research objectives, 223 women completed the inclusion criteria checklist, FSFI, and the DASS anxiety questionnaire. Women who had an FSFI score of less than 28, as well as moderate or severe DASS stress met the inclusion criteria. Meanwhile, 152 women did not meet the inclusion criteria, and 11 women declined to participate. As a result, the remaining 60 women who had the inclusion criteria were randomly divided into the control or the intervention groups using simple individual randomization with an envelope containing a piece of paper titled A or B (Figure 1). By choosing a certain number of cards or letters for the intervention group and the same number of cards for the control group, the two groups of cards were combined. A card was removed, its allocation was noted, and after it was removed, the card was returned to all the other cards. The cards were then merged once more as a new card was pulled out. Considering the sample size, this procedure was continued until a random sequence was reached. The study was also a three-blind study, i.e., the participants, the researcher, and the analyst were unaware of the grouping. To accomplish this, the shape of the turmeric and placebo capsules were similar (the intervention group used 300 mg of turmeric extract daily for 4 weeks, while the control group used a placebo containing 500 mg of starch and no effective turmeric). Furthermore, the researcher was unaware of the group of participants when analyzing the results. The pharmacist was asked about the type of capsule used in each of the study groups after the research and analyses were completed. The participants were asked to fast on the third day of their menstrual period for blood sampling. In both groups, serum adiponectin levels, as well as hormonal levels such as estradiol, progesterone, and prolactin, were measured. The capsules were completed and followed by all women in the control and intervention groups. Similar to previous studies, no side effects were observed in the intervention group following the use of turmeric extract. Both groups completed the DASS stress questionnaire and FSFI four weeks after the intervention. The two groups were compared in terms of the pre-and post-intervention scores, steroid hormones, blood glucose, lipoprotein, and body mass index. After completing the DASS questionnaire, the stress level of three participants in the control group was discovered extremely high due to the COVID-19 pandemic. After excluding them from the trial, only the data of 30 women in the intervention group and 27 women in the control group were used for statistical analysis.

The serum levels of adiponectin, estradiol progesterone, and prolactin were estimated using a human ELISA kit (Zell Bio GmbH, Ulm, Germany); the intra-assay coefficient of variation (CV) was 6.3% and the assay sensitivity was 0.1µg/ml. A standardized checklist was used to gather anthropometric and laboratory data.

Participants in the intervention group received 300 mg of turmeric extract per day for four weeks. A pharmacist at Shahid Beheshti University, extracted and concentrated turmeric. In addition, those in the control group received a placebo containing only 500 mg of starch (turmeric and placebo capsules were comparable in form and size).

The data were analyzed statistically in SPSS-14 (SPSS Inc .Chicago, IL, USA). The Kolmogorov-Smirnov test was used to examine the normal distribution of the variable, and the chi-square was employed to test the homogeneity of the two groups in terms of educational attainment and job. The pre-and post-intervention scores and values were compared between the groups through the paired t-test and the independent t-test. The significant level in all tests was considered to be $P<0.05$.

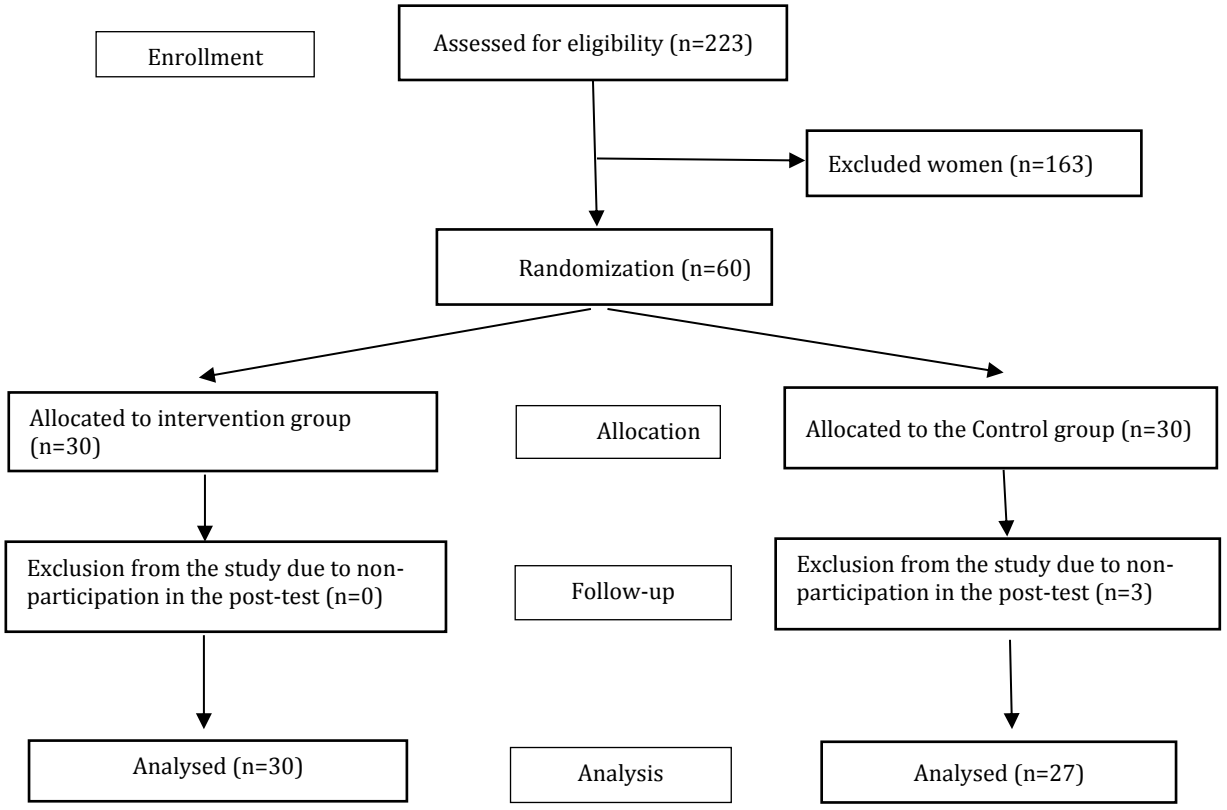


**Figure 1.** CONSORT flow diagram of participants selection

## Results

A total of 57 participants completed this study; 30 in the intervention group and 27 in the control group (Figure 1). Three participants from the control group were excluded from the study due to being infected with the coronavirus. There was no significant difference between the two groups in terms of demographics and clinical parameters (Table 1).

There was no significant difference between the two groups in terms of the pre-intervention mean/median of adaptation (0.488), estradiol (0.529), and progesterone (0.530). Nevertheless, the mean/median of adiponectin, progesterone, and estradiol significantly increased in the intervention group after the intervention ($P=0.005$, $P<0.001$, $P<0.001$) (Table 2). As shown in Table 2, there was no statistically significant difference in the pre-and post-intervention prolactin levels in the intervention group ($P=0.783$).

**Table 1.** Comparison of demographic and clinical characteristics between the two groups

| Variables | Intervention group | Control group | P-Value |
|---|---|---|---|
| **Age (years)** | 26.93±6.77 | 27.73±6.70 | P =0.729[b] |
| **Weight (kg)** | 63.40±5.03 | 62±5.64 | P =0.480[b] |
| **Height (meter)** | 1.63±0.05 | 1.62±0.06 | P =0.736[b] |
| **Marital age (years)** | 21.73±4.26 | 22.40±4.40 | P =0.677[b] |
| **BMI (kg/m²)** | 23.63±0.92 | 23.31±0.89 | P =0.329[b] |
| **Marital duration (year)** | 5.73±4.86 | 7.13±8.11 | P =0.527[b] |
| **Educational level, N (%)** | | | |
| Elementary and middle | 15 (53.3) | 12(40) | P =0.464[c] |
| Diploma and university | 12 (46.7) | 18(60) | |

[a] All data are presented as mean ± SD or N (%); [b] Independent T test; [c]Chi-square test

**Table 2.** Comparison of adiponectin and steroidal hormones between the two groups before and four weeks after the intervention

| Parameters | Intervention group | Control group | P-Value |
|---|---|---|---|
| **Adiponectin** | | | |
| post-intervention | 18.56±2.76 | 20.36±1.16 | P=0.015[b] |
| Pre-intervention | 18.10±1.78 | 18.38±1.82 | P=0.331[b] |
| P-value | P=0.488[c] | P=0.002[c] | |
| **Estradiol** | | | |
| Post-intervention | 73.53±1.41 | 76.0±1.33 | P<0.001[b] |
| Pre-intervention | 74.16±5.54 | 71.91±4.90 | P=0.052[b] |
| P-value | P=0.529[c] | P=0.048[c] | |
| **Progesterone** | | | |
| Post-intervention | 12.40±1.25 | 13.91±1.51 | P<0.001[b] |
| Pre-intervention | 12.40±0.79 | 12.36±0.86 | P=0.80[b] |
| P-value | P=0.945[c] | P=0.003[c] | |
| **Prolactin** | | | |
| Pre-intervention | 9.48±0.92 | 9.52±0.89 | P=0.783[b] |
| Post-intervention | 9.71±0.604 | 9.70±0.61 | P=0.772[b] |
| P-value | P=0.530[c] | P=0.560[c] | |

[a]All data are presented as mean ± SD or N (%); [b] Independent T test; [c] Paired t-test

Additionally, there was no significant difference between the two groups in terms of the pre-intervention levels of FBS (P=0.933), cholesterol (P=0.922), triglyceride (P=0.308), LDL (P=0.917), and BMI (P=0.572). However, there was a significant difference between the two groups in FBS (0.0.001), cholesterol (P<0.001), cholesterol (P=0<0.001), triglyceride (P=0.003), LDL (P=0.001), and BMI (P=0.001) after the intervention (Table 3).

But, there was a significant difference in these data, except triglyceride, in the control group (Table 3).

The study results also indicated that there was no significant difference between the two groups in the pre-intervention sexual function (P=0.81) and stress (P=0.803) (Figure 2), but asignificant difference was observed between the two groups after intervention (P<0.005, P<0.005) (Figure 2).

**Table 3.** Comparison of glucose and lipid between the two groups before and four weeks after the intervention

| Parameters | Intervention group | Control group | P-Value |
|---|---|---|---|
| **FBS** | | | |
| Post-intervention | 93.06±4.11 | 90.6±3.52 | P=0.001 [b] |
| pre intervention | 92.93±4.44 | 93.20±4.70 | P=0.741 [b] |
| P-value | P=0.933 | P=0.048 | |
| **Cholesterol** | | | |
| Post-intervention | 141.26±12.49 | 137.66±12.93 | P<0.001 [b] |
| Pre intervention | 141.73±13.39 | 142.80±13.52 | P=o.157 [b] |
| P-value | P=0.922 | P=0.297 | |
| **Triglyceride** | | | |
| Post-intervention | 169.53±10.98 | 162.53±9.14 | P=0.003 [b] |
| pre intervention | 170±13.12 | 173.06±13.39 | P=0.014 [b] |
| p-value | P=0.308 | P=0.311 | |
| **LDL** | | | |
| Post-intervention | 108±10.98 | 103.33±10.40 | P=0.001 [b] |
| pre intervention | 104.20±11.53 | 107.20±10.13 | P=0.092 [b] |
| P-value | P=0.917 | P=0.031 | |
| **BMI** | | | |
| Post-intervention | 23.63±0.92 | 23.30±0.92 | P=0.001 [b] |
| pre intervention | 23.31±0.89 | 23.28±0.81 | P=0.673[b] |
| P-value | P=0.572 | P=0.968 | |

[a]All data are presented as mean ± SD or N (%); [b] Independent T test; [c] Paired t-test

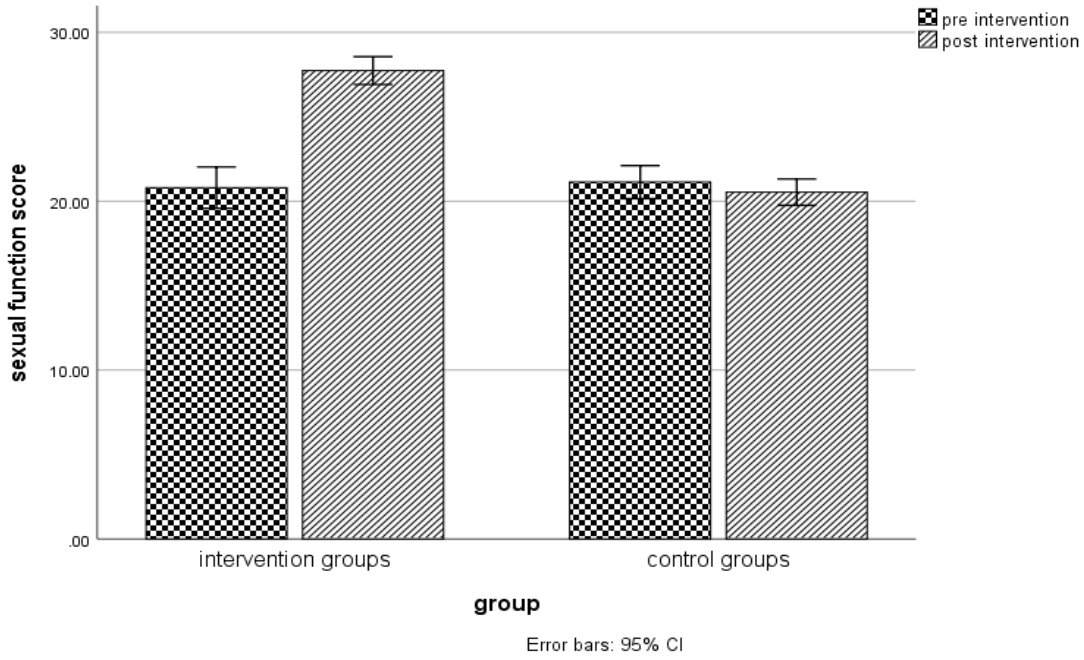


**Figure 2.** The difference in the mean score of sexual function before and after the intervention in the two groups

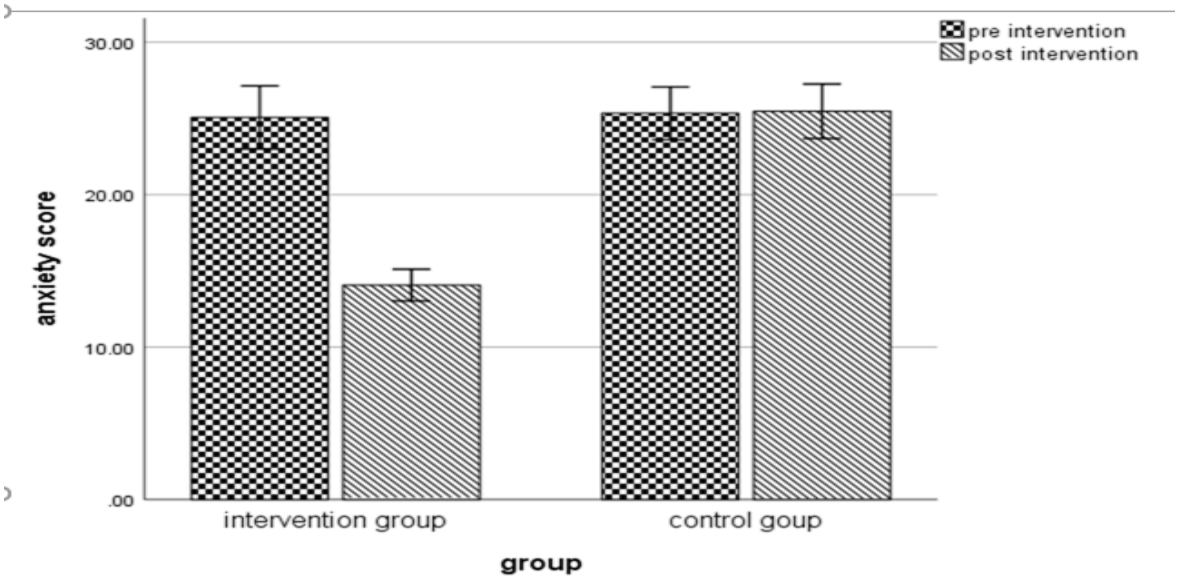


**Figure 3.** The difference in the mean score of anxiety before and after the intervention in two groups

## Discussion

This study was conducted to investigate the effect of turmeric extract on serum adiponectin levels, steroid hormone profiles and sexual function in stressed women. The study results indicated that adiponectin levels increased after consuming turmeric extract. The expression of the adiponectin gene increases following consumption of curcumin, according to Yu-na B et al. (2013) (13). In another study, Weberg et al. discovered that taking curcumin for four weeks increases serum adiponectin levels. Panahi et al. reported that adiponectin secretion increased after treating fat cells with 100 mg/kg of turmeric (17). The results also demonstrated that turmeric extract resulted in increased estrogen and progesterone, which is consistent with the findings of Thakur et al. (2009). According to our findings in this study, the alkaloid and flavonoid content of turmeric alcoholic extract raises the level of estradiol, causing the uterus and ovaries to develop in size (18). Turmeric extract exerts pro-apoptotic, pro-necrotic, and anti-proliferative actions in mice ovaries, and it protects oogonia cells from stress produced by FSH decrease. It is not understood how turmeric affects the reproductive system. Nonetheless, gonadotropins and ovarian steroids, as well as peptide hormones such as leptin and adiponectin, have been associated with the growth and development of follicular blood vessels in this study.

Furthermore, turmeric extract did not enhance levels of estradiol and progesterone in the groups receiving adiponectin antagonist injections in this study. According to these studies, turmeric extract raises estrogen and progesterone levels via adiponectin. Turmeric is also a phytosteroid that can exhibit such an effect on the hypothalamus-pituitary-ovarian axis (19). Curcumin raises serum gonadotropins by reducing oxidative stress and increasing antioxidant enzyme activity (20). The study results also showed an increase in gonadotropins due to a rise in estrogen and progesterone hormones in both males and females. Curcumin has also been reported to play a vital function in estradiol secretion and antral follicle expansion via boosting FSH secretion (21).

Turmeric extracts improve sexual performance (22). Several studies have found a relationship between greater levels of steroid hormones and increased sexual performance. Most studies have found a positive relationship between estradiol levels and sexual desire (23).

Furthermore, the study findings showed that turmeric consumption reduced stress levels. According to Khader et al., metformin boosted adiponectin levels in stressed mice, which consequently decreased stress levels. Turmeric stimulates adiponectin release, which crosses the

blood-brain barrier and increases dopamine secretion. The brain mediates adiponectin's anti-stress function. The activation of Adipor1 and Adipor2 in the brain can activate Ampk while inhibiting the mitogen-activated protein kinase (p38MAPK). The p38MAPK signaling pathway mediates adiponectin-induced phosphorylation of glycogen synthesize kinase 3 (GSK-3). Activation of GSK-3 worsens mental disorders (24-25). Stress reduction naturally leads to enhanced sexual performance. Sexual disorders such as problems with sexual desire, arousal, and orgasm affect many stressed-out women. Catecholamine levels rise in response to stress. These catecholamines stimulate the expression of dopamine receptors in the brain. As a result, increased cortisol levels following stress affect sexual performance by activating catecholamine neurons in the brain. Stress and estradiol have dramatically opposed effects (26-27). The study results indicated that the post-intervention fasting blood sugar and LDL were significantly lower in the intervention group than in the control group, which is consistent with the results of some previous studies.

Recent studies have shown that adiponectin levels and insulin sensitivity are lower in diabetics than in healthy individuals (28-29). In this regard, the study findings are consistent with those of Satarizadeh et al. (2021) and Azhari et al. (2019) (29-30). The results of this study also revealed a significant difference in the pre-and post-intervention levels of cholesterol, triglyceride, and BMI in the intervention group. However, there was no statistically significant difference in the post-intervention levels of these variables between the control and intervention groups. In this regard, the study findings are not consistent with the results of Azhari et al. (2019). and Sattari et al. (2021). This could be because changing these variables required a longer intervention. Furthermore, the determined sample size could not help to achieve this purpose. Adiponectin levels are inversely correlated with anthropometric measurements, especially abdominal obesity, and lipid profile characteristics like triglycerides, total cholesterol, and low-density lipoprotein (LDL). Most reviewed studies indicate a stronger relationship between lipid serum and adiponectin levels in patients with metabolic syndrome (31). The serum adiponectin level is lower in patients with diabetes, hyperlipidemia, and cardiovascular diseases who suffer from blood lipid disorders (32). Our study was the only triple-blind study in this era. Sampling in the current study was done in the follicular phase, which might be better done in the luteal phase as well. Also, based on the results of the present study, turmeric extract can be used by women under stress to improve sexual function and the level of sex hormones. In addition, we can use turmeric extract for fat and blood sugar control.

## Conclusion

The study findings suggested that turmeric extract can enhance adiponectin levels and as a consequence estrogen and progesterone levels. Also, it was found that turmeric can enhance sexual function. It is especially significant in stressed populations whose adiponectin levels are low. Therefore, healthcare providers can recommend consuming turmeric-containing foods to women for improvement of their sexual function.

## Declarations

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## Conflicts of interest

The authors declared no conflict of interest.

## Funding

Financial support was done by Tarbiat Modares University, Tehran, Iran.

## Ethical approval

The study protocol and its ethical consideration were approved by the Ethics Research Committee of Tarbiat Modares University (IR.MODARES.REC.1397.206).

## Authors' contribution

NT contributed to the conception, drafting the manuscript and language editing of the manuscript. ESS contributed to the conception, data collection and Drafting the manuscript. AK and FM contributed to the conception, data collection, statistical analyses and interpretation of data. All authors read and approved the final

manuscript and agreed to be accountable for all aspects of the work.

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