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Effect of Tinospora cardifolia (Giloy) and dietary changes in polycystic ovarian syndrome (PCOS)-An observational study

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common endocrine dysfunction reducing infertility of females of the reproductive age group. Current study aimed to present the perfect dietary pattern and role of Tinospora cardifolia (Giloy) for females with polycystic ovary syndrome to alleviate their symptoms and signs of infertility.

Methods: An observational study was done for 3 months on subjects selected from the outpatient department of a tertiary care hospital in Lucknow, Uttar Pradesh. Patients were followed for three months to asses the outcome of dietary change and Tinospora cardifolia.

Results: 50 patients were included in the study who attended the endocrinology outpatient department of a tertiary care center in Lucknow. All were female patients. Dietary advice by a dietician and supplementation of Tinospora cardifolia was advised to all subjects. After a follow-up period of 3 months, it was observed that consuming Giloy and more high-fiber foods and lean protein and limiting refined carbohydrates and sugary foods are playing a vital role in the clinical picture and laboratory findings of PCOS. The use of Giloy and change in women's diet resulted in increased fertility of the females. This study demonstrates the effect of Giloy and the type of diet that is deemed helpful in the clinical and laboratory picture of the syndrome.

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Conclusion: In the future, more research should be conducted on a larger population with PCOS and for a longer period, during which subjects would be given a specific diet and Giloy products. It would also be important to compare diet to mild exercise and dietary supplementation. Giloy increases the libido and fertility in PCOS patients.

Keywords: Tinospora cardifolia, Polycystic ovarian syndrome, amenorrhea, Giloy and PCOS, Infertility, libido.

Introduction

Polycystic ovary syndrome (PCOS) is an important issue in female patients of infertility due to an imbalance in hormonal profile. There is the formation of polycystic ovaries, raised testosterone values, and the occurrence of infertility [1]. It seems that 5-10% of females in the age group between 18-44 years may suffer from PCOS [2]. There are several high-risk factors for PCOS development like hereditary and environmental factors [3]. Menstrual irregularities, infertility, hyperglycemia, raised blood levels of masculinizing hormones, hyperinsulinemic metabolic syndrome, and endometrial cancer are the various characteristic features of PCOS [4]. Hyperandrogenism symptoms may include, menstrual irregularities, hirsutism, acne, and infrequent or absent ovulation [5]. Elevated levels of luteinizing hormone (LH) or raised blood insulin levels are assumed to be the main contributors to the etiology of PCOS [6]. Such patients generally have extensive clinical management, including lifestyle modification and pharmaceutical interventions. Treatment modalities for polycystic ovarian syndrome are fewer. The symptoms of PCOS may be treated by symptomatic treatments [7]. The main aims of management in PCOS are restoration of fertility, regularization of menstrual cycle, improvement in insulin resistance (IR), acne and hirsutism management, and prevention of endometrial hyperplasia[8]. Hot flashes, joint or muscle

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discomfort, arthritis, mood swings, irritability, bloating, and melancholy are psychological and physiological side effects of contemporary PCOS treatment [9].

Medicines obtained from natural resources are impressive substitute treatments with a familiar mode of action for the production of a powerful, safe, and cost-effective therapeutic agent for this ailment [9]. Till now, there are fewer scientific basis for the claims that complementary and alternative treatments are both safe and effective. This mandates the evaluation of some unconventional methods for the prevention and treatment of PCOS, like medicines [7]. To date, Tinospora cordifolia (TC) is one of Ayurveda's most popular medicinal plants used in several disorders [10]. In Ayurvedic and ethnic medicine, tinospora cardifolia has many medicinal uses because of its minimal side effects and a vast range of beneficial effects, like arthritis, leprosy, fever, periods, allergies, diabetes, stress, and malaria. The stem of TC is used as a thirst quencher, diuretic, iron source, and vitamins, and cure for jaundice, and stomachic bitterness. Some pieces of evidence have also suggested that stem extract is useful in skin disorders. In combination with other medicines, TC acts as an antidote for scorpion stings and snakebites [11]. TC has been also used in the treatment of cough, wounds, asthma, and pneumonia. TC has also benefitted patients of cancer and protects nerve cells, enhances the immune system, reduces cholesterol, and resistance to diabetes, and protects the liver. It was also found helpful in the faster healing of diabetic foot ulcers and the mitigation of some of the side effects due to chemotherapy and radiation [10]. As an anti-inflammatory herb, TC is considered extremely beneficial for PCOS because insulin dysregulation and ovarian cysts both have similar etiology, i.e., chronic mild inflammation in the tissues. Reduction of IR enhances metabolism and all tissues are stimulated naturally [12]. The important constituents of TC include alkaloids (choline, jatrorrhizine, tinosporine, magnoflorine, berberine (BER), palmatine (PAL), tembeterine), flavonoids (quercetin, luteolin, and kaempferol), terpenoids, steroids, sesquiterpenoids,

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glycosides, polysaccharides, essential oils, and a mixture of fatty acids [13]. Syringin, berberine, and rumphioside-I alkaloids were studied, and in silico analyses were found to significantly inhibit insulin receptor substrate-1 (IRS-1) and IRS-2 receptors with the help of the antagonistic ligand. When docked against the human androgen receptor 1E3G, BER and PAL were found superior to other compounds. Isoquinoline alkaloids (BER and PAL) may act against several diseases such as virtual screening of an alkaloid from the stems of TC for PCOS led to a scientific evaluation [14]. Also, BER positively restores serum levels of hormones and decreases resistance to insulin. In PCOS, apoptosis and structural damage of both ovaries were improved and repaired by BER treatment. BER's doe's proliferation of granulosa cells and death were alleviated by preventing the PI3K/AKT pathway [15]. This is hoped that these medications will have effective results in PCOS after thorough preclinical and clinical testing [16]. The Food Safety and Standards Authority of India (FSSAI) mentioned that the root and stem of Tinospora cardifolia that it has a nutritional value in the form of decoction, powder, sattva (satva), and extract in a quantity ranging from 0.5 to 10 g [17]. The primary purpose of conducting this study was to evaluate the efficacy of TC in mitigating the symptoms of PCOS and restoration of fertility.

2. Materials and Methods

The current study was an observational study conducted in the outpatient department (OPD) of a tertiary health care center in Lucknow. Patients attending the endocrinology OPD were enrolled in the study because patients with PCOS regularly come in this OPD. Parallel to the endocrinology OPD, dietary advice by an expert dietician was also given to the patients in the hospital. Female patients with symptoms of PCOS were notified. A total of 50 subjects were enrolled in the study. Dietary advice with more high-fiber foods and lean protein, and limiting refined carbohydrates and sugary foods was given to the patients along with extract

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of Tinospora cardifolia provided in the form of stem juice and followed for three months. Patients were regularly assessed for improvement in PCOS symptoms, return of fertility, and laboratory parameters.

2.1. Formulation of Guduchi Satva

The fresh TC stems were used to make guduchi satva (water extract by following FSSAI/Ayurvedic-approved method of preparation).

2.2. Establishment of PCOS Model

Oral administration of TC preparations continued and assessment of the preventative benefits of TC extracts in PCOS was done regularly. The patients were weighed on each monthly follow-up. Blood glucose levels were monitored and an Oral Glucose Tolerance Test (OGTT) was also carried out. Measurements of insulin, testosterone, progesterone, estradiol, cholesterol, LH, FSH, and triglycerides were taken. Ultrasonography (USG) was also done to see the shape and structure of the bilateral ovaries.

2.3. Menstrual Cycle Monitoring

To measure the variations in the menstrual cycle of the subjects, proper history and ultrasonography whole abdomen were done.

2.4. Change in Body Weight

Regular variations in the body weight of female patients with PCOS were assessed every month. Body weight was noted on initial evaluation and noted further in the follow-ups for its decrease or increase.

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2.5. Measurement of Fasting Blood Glucose (FBG) and Oral Glucose Tolerance Test (OGTT)

On day 30, for the OGTT measurement, the patients were advised to take 75 grams of glucose. Blood samples were withdrawn to assess sugar level after two hours. The fasting blood glucose was also measured on days 1 and 30.

2.6. Blood Collection, Collection of Plasma, and Detection of Biochemical Indexes

We assessed the serum values of the fasting lipid profile with the help of a biochemical analyzer, along with fasting insulin (FINS) levels, followed by the calculation of HOMA- IR, HOMA-Beta, and QUICKI. These are the most common methods/formulas used in epidemiological studies. Serum estradiol, progesterone, and testosterone levels were also assessed.

2.7. Measurement of Size and Morphological Changes in the Ovaries

In regular follow-ups of one month with an assessment of USG whole abdomen was done to look for the shape and size of ovaries.

2.8. Statistical Analysis

Statistical analysis was performed, and the data were fed into an Excel sheet. Results were interpreted. Data were presented as mean ± SEM. The unpaired T-test was used to analyze the categorical data, while the paired T-test, one-way analysis of variance (ANOVA), was used to analyze the continuous data. Statistical significance was assumed when the p-value was less than 0.05.

3. Results

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3.1. Body Weight

Patients who took TC satva had a significant ($p < 0.001$, 0.03, and 0.21) reduction in BW as compared to initial values before treatment started (Table 1).

Table 1 shows the effect of TC satva on weight

% of patients	BW before treatment (Kg)	BW after 3 month of treatment (Kg)	P value
45% Patients	66.2-70.3	59.44-62.33	<0.001
20% Patients	60.33-66.21	55.21-58.22	0.03
35% Patients	55.34-60.33	50.1-54.76	0.021

3.2. Fasting Blood Glucose Level

On day 1, the fasting blood glucose level was higher in 77 % of subjects. Highly significant ($p < 0.001$) reductions in BG were observed in groups of patients treated with TC satva on day 30 (Table 2).

Table 2 shows the effect of TC satva on fasting blood sugar

% Of Patients with High Blood Sugar levels	FBS day 1 (Mg/dl)	FBS day 30 (Mg/dl)
30%	140-150	120-130

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20%	150-170	120-140
15%	170-200	140-160
12%	200<	150-160

3.3. Oral Glucose Tolerance Test

On day 30, 1 hr OGTT of TC satva treatment significantly ($p < 0.01$) elevated blood glucose values compared to 0 h OGTT of TC satva, but it was normal after 2 h OGTT. The 2-h OGTT results indicate that TC treatment for more than 30 days significantly improves glucose levels in PCOS patients.

3.4. Hormonal Profile

In all TC treatment subjects, there was a decrease in serum testosterone, but the highest doses of satva brought it down to nearly normal levels. The maximum dose (400 mg/kg) of TC satva significantly increased estradiol levels. Treatment with TC extract prominently raised ($p < 0.01$) serum progesterone levels (Table 3).

3.5. LH and FSH Level

LH and FSH levels were found to be decreased in patients who were given TC extracts compared to initial values for their condition. The LH/FSH ratio was initially increased (2.87). In all TC extract treatment subjects, the FSH was higher than LH (Table 3).

Table 3 shows the effect of TC satva on hormones

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Hormones	Blood levels on day 1	Blood levels after 3 month of treatment	P value
S. Testosterone (70% patients) nmol/L	10.34-12.54	5.22-6.23	<0.01
S. Estradiol (67.2% patients) pg/ml	17.76-20.78	28.22-30.98	0.023
S. Progesterone (81% patients) ng/ml	5.22-6.21	7.65-8.66	<0.01
S. LH (70% patients) mIU/ml	6.42	3.32	0.05
S. FSH(78% patients) mIU/ml	2.23	6.43	<0.001

3.6. Lipid Profiles

All PCOS patients treated with TC extracts had significantly reduced serum cholesterol and triglyceride levels compared to their initial values before the study ($p < 0.01$ to $p < 0.001$) (Table 4).

Table 4 shows the effect of TC satva on the lipid profile

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Lipid profiles	Blood levels on day 1	Blood levels after 3 months of therapy	P value
Total cholesterol (gm/l) (87% patients)	200.22-250.89	150.21-170.87	<0.01
Triglyceride (gm/l) (90% patients)	190.90-288.88	140.99-200.87	<0.001

3.7. Insulin Profile

Serum insulin was significantly reduced ($p < 0.001$) in the TC-treated patients. Similarly, the HOMA-IR index was highly significantly ($p < 0.001$) reduced by TC treatment in patients (Table 5).

Table 5 shows the effect of TC satva on fasting insulin

% of patients with high insulin	Fasting Insulin on day 1 (iu/ml)	Fasting Insulin after 3 month of therapy (iu/ml)	P-Value
67% of patients	1.4-1.6	0.5-0.78	<0.001

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3.7-Menstrual cycle

Almost all the subjects of PCOS had irregular menstrual cycles. After a three-month therapy with TC satva and dietary change, ultrasonography was done and menstrual improvement was asked during the follow-up of the patients. 85.56% of PCOS patients were having normalization of ovarian size and 90.78% were returned to their normal cycle.

4. Discussion

Metabolic disturbances are generally linked with polycystic ovarian syndrome, a frequent reproductive condition. Insulin resistance, dyslipidemia, and diabetes mellitus are the various conditions that are commonly associated with PCOS. Obesity, genetic predisposition, inflammation, insulin resistance, and oxidative stress are the theoretical conditions that demonstrate PCOS [18]. Patients with PCOS generally experience ovarian and neuroendocrine dysfunction [19,20]. Insulin increases the secretion of androgens from ovarian stromal and thecal cells. An increase in ovarian androgen formation because of insulin resistance and hyperinsulinemia is the cause of hyperandrogenism in PCOS. To date, the exact etiology behind PCOS is still unknown, but its primary features can be replicated in a mouse model using DHEA [21-23].

As TC is a potent anti-inflammatory herbal drug, it was expected that TC extracts would benefit in the correction of insulin balance and decrease the chances of having ovarian cysts. TC will act as an herbal agent for rejuvenation, and it might enhance body tissues and improve metabolism [12]. In the current study, the effects of TC extracts on ovarian weight, body weight, ovarian shape, and insulin sensitivity were observed and noted. Increases in ovarian weight, body weight, LH, testosterone, glucose, and insulin resistance were indicators of compromised fertility and reproductive health in PCOS patients. It was observed that the TC

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extracts regain normal body weight, decrease insulin resistance, and decrease PCOS-related dyslipidemia. It also balances and controls the values of hormones like FSH, LH, progesterone, estradiol, and testosterone. The morphological studies support that the TC extracts prevent variations in the cellular, tissue, and organ systems of the body. Regaining normal circulatory levels of estrogen, testosterone, progesterone, and gonadotrophins may be due to TC's restorative impact on the patient's menstrual cycle, as found in the present study. Ovarian functions, like follicular maturation and hormonal imbalance, are observed to be normalized by a regular menstrual cycle, which is under the control of the above hormones [24].

We have several supporting pieces of evidence that link PCOS and overweight [25]. Elevation in levels of growth hormone production and its release by the anterior pituitary gland may have stimulated the secretion of insulin-like growth factors (IGFs) I and II, which most likely occurred because of the TC extract's effect on the metabolic pathway [26]. This hormone is necessary for enhancing the cellular absorption of amino acids, skeletal muscle development, and regulation of lipolysis. In contrast, satva significantly decreased the BW of PCOS subjects by restoration when compared to their initial values. The TC extract-taking PCOS patients also lose the significant extra weight that was gained initially ($p < 0.01$). After 6 months of treatment, the patient's body weight had approximately come to normal. This observation supports, what has been found previously, as TC therapy controls energy metabolism, loss of lipids, cellular homeostasis, and hypoglycemia [13,25].

Compared to initial values, patients taking TC extracts had significantly decreased blood glucose values. Therapy with TC satva resulting in hypoglycemia may be because of the activation of glucose 6-phosphatase and normal values of liver glycogen, inhibition of gluconeogenesis, inhibition of glycogenolysis, and suppression of oxidative stress [27]. Reported suppression of peripheral glucose release in hyperglycemia, insulin-mimicking and

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insulin-releasing actions, glucose uptake and insulin secretion have been observed in TC's isoquinoline alkaloids, magnoflorine, jatrorrhizine, and palmatine [28, 29].

On day 30, 1 h OGTT of TC satva therapy elevated glucose values as compared to 0 h OGTT of TC satva, but it was found normal after 2 h OGTT. This signifies that there was an inadequate quantity of insulin secreted upon glucose load. To tackle with hyperglycaemic effect of diabetes, reducing hepatic phosphorylase activity and enhancing glucose absorption by peripheral tissues and organs, like the liver, may be good [30], and it may be the mechanism of action of TC extracts.

Estradiol and progesterone values were lower in the PCOS group and low progesterone levels lead to anovulation. Raised plasma androgen and reduced estrogen and progesterone levels in the blood have been found in PCOS subjects [9]. Hyperandrogenism is due to the over-formation of androgens from ovaries due to insulin resistance with hyperinsulinemia in PCOS patients. This is believed that theca and stroma cells, IGF-1 receptors are the mechanism by which insulin controls ovarian androgen formation [31]. The growth hormone IGF-1 enhances granulosa cell aromatase release and formation [32] and acts in association with FSH and LH, controlling the formation of aromatase there.

Elevation in androgen values can also raise FSH receptors in PCOS patients which further decreases serum FSH levels as a result of negative feedback. Prior research has associated PCOS with insulin resistance because of abnormally high LH or low FSH levels. Both the LH and testosterone values increased due to disruption of the normal hypothalamic–pituitary–gonadal axis, which is the etiology behind the condition [33]. LH reduces progesterone values and raises androgen levels by stimulating testosterone secretion from theca cells via the PI3K/Akt pathway, which oversupplies the functions of the 17-a hydroxylase enzyme, catalyzing the formation of androgens by progesterone [34]. All TC extract therapy patients

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have a reduction in serum testosterone, but the maximum doses of satva brought it to almost normal levels.

Maximum satva raised estradiol levels compared to prior values. All therapy with TC extracts showed a significant rise in serum progesterone levels. LH and FSH levels were reduced due to TC extracts as compared to initial levels before the start of the therapy. In all TC extract therapy received patients, the FSH was more than LH and it caused the ratio of LH to FSH to significantly dropped. The blood serum values of LH and FSH were returned to normal.

Biochemical evaluation of PCOS subjects found dyslipidemia, with a disturbed lipid profile out of whack: higher triglycerides (TG), raised total cholesterol, decreased HDL, and raised low-density lipoprotein (LDL) [9]. Dyslipidemia, with higher TGs and reduced HDL cholesterol, is commonly found in PCOS. Dyslipidemia of PCOS does not discriminate by weight. The syndrome is linked with a considerably higher risk of having type II DM as a result of the synergistic action of obesity and insulin resistance. Subjects with PCOS may have dyslipidemia because of several aetiologies. IR plays a significant contribution by enhancing lipolysis and changing the formation of hepatic lipase and lipoprotein lipase. It was also observed that a significant reduction in blood cholesterol and TG levels was there in the TC treatment-taking patients with PCOS. It was a very interesting observation that there was a normalization of TG and cholesterol levels in the patients taking TC. Prior studies have reported that the lipid-lowering feature of TC's active components, including its alkaloids, flavonoids, saponins, glycosides, and tannins, may have caused the decreased BW and lipid profile [13].

Hyperinsulinemia/hyperandrogenism together is found in PCOS, IR can significantly elevate levels of blood proinflammatory cytokines [35]. The features of PCOS, like raised levels of androgens and irregular or absent menstrual cycles, may be due to IR, which also increases the

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chances of hyperlipidemia, diabetes mellitus, and cardiovascular disease [36]. So, reducing insulin resistance may be one of the most important parts of management which will further improve reproductive health. Treatment by TC resulted in a significant reduction in blood insulin values, which explains the reversal of insulin resistance. In PCOS there was an increase in the HOMA-IR index, and it was then reversed by TC treatment. A highly significant decrease in serum insulin value was found after TC therapy.

The lower doses of TC satva significantly improved QUICKI. The path mechanism by which the active chemical components of TC raise muscle glucose absorption is favored by the Insulin Sensitivity Index QUICKI. Therapy with TC explains a dose-dependent modification in the function of beta cells, which is reflected in the HOMA-Beta values [37]. The above results are similar to earlier observations that TC decreases fructose-induced rise in blood sugar, insulin, and triglycerides. The berberine alkaloid of the TC plant stem has been shown to significantly increase glucose tolerance. Therapy with berberine significantly improves insulin sensitivity, decreases fasting plasma glucose, and decreases LDL-C in type II diabetic patients, which explains its potent antihyperglycemic and hypolipidemic activity.

Silico investigations observed that the alkaloids berberine, syringin, and rumphioside-I as antagonistic ligands maximumly prevent IRS1 and IRS2 receptors. Isoquinoline alkaloids (such as berberine and palmatine) do significant actions in warding off a vast number of disorders. Alkaloid extracted from TC stems has been evaluated and screened for the therapy of PCOS [14]. Berberine corrects IR and serum hormone values in PCOS. Berberine treatment also regains ovarian apoptosis and morphological disturbances. Berberine's acts on the increase of granulosa cells and death were mitigated by blocking the PI3K/AKT pathway [15]. After several animal and human researches, it was possible that these drugs could be used in the treatment of PCOS [16].

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Subjects given TC appeared to regain normal health. After management of PCOS patients with TC, restoration of follicle numbers was seen and ovaries were saved from oxidative stress [38]. TC therapy decreased ovarian hypertrophy, ovarian weight, and appearance and resulted in normal ovaries. Similar findings were also noted in the study by [37, 38]

Cystic follicles, as opposed to growing follicles and the corpus lutea, are commonly found in the PCOS ovaries depicting that physiological actions in the ovaries are being prevented. It was also seen that a marked reduction in cyst number was also there. Primitive follicle numbers in the ovaries of the treatment groups were, thus, considerably higher [39].

5. Conclusions

The observations of the present study show that patients with PCOS treated with TC preparations as nutritional supplements maintained a normal menstrual cycle and restored normal weight. TC satva was observed to be the most effective in reducing blood sugar levels, testosterone, LH/FSH ratio, OGTT, insulin resistance, lipid profile, and diameter of ovary and weight, and reducing granular changes and disease severity. Therapy of PCOS patients with TC satva raised the values of progesterone and estrogen, insulin sensitivity, the number of follicles, and FSH. Based on these results, we conclude that TC preparations as nutritional supplements may have good effects in the therapy and management of PCOS-related complications and conditions. More research is needed to set the molecular mechanism of action of TC extracts for generalization and possible clinical utilization.

Conflict of Interest-none

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