Int J Trans Res Ind Med 2021, 3(3): (P) 01 - 06

Research Article

ISSN 2582-0109

International Journal of Translational Research in Indian Medicine
www.ijtrim.com
Volume 3, Issue 3 – 2021

EVALUATION OF SIDDHA FORMULATION THUMATTIKKAI MEZHUGU (TM) IN POLYCYSTIC OVARIAN SYNDROME MODEL IN WISTAR RATS

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. Its cause is unknown and it remains the most enigmatic of reproductive disorders. The medical management of this problem requires a multidisciplinary approach. Because the primary cause of PCOS is unknown, treatment is directed at the symptoms. The use of herbal medicinal products and supplements has increased tremendously over the past three decades with not less than 80% of people worldwide relying on them for some part of primary healthcare. Few treatment approaches improve all aspects of the syndrome, and the patient's desire for fertility may prevent her from seeking treatment despite the presence of symptoms. Conventional therapy for the management of PCOS offers symptomatic treatment and hence the possibility of recurrence is very frequent. Drugs like metformin also has side effects such as nausea and vomiting, diarrhoea, bloating and abdominal pain, loss of appetite and metallic taste, deficiency of vitamin B12, and lactic acidosis. Siddha drug like Thumattikkai mezhugu (TM) indicated for the treatment of PCOS but still now there is no proven documentary evidence revealing its efficacy, hence the main objective of the present study is to evaluate the potential of TM against dehydroepiandrosterone (DHEA) induced PCOS in rat model. From the result analysis of the present investigation it was clear that the weight of ovary sample belongs to group II rats shown progressive increase when compare to group I. Treatment with TM at both the dose level shown pronounced decrease in the weight of the ovaries. From the immunoassay analysis it was predicted that FSH level of group II rats shown significant decrease when compare to control group I. Treatment with TM to group III and IV at the dose of 200 and 400 mg/kg shown promising increase in the level of FSH hormone. It was concluded from the data's obtained from the study that the siddha formulation like Thumattikkai mehugu may be considered as drugs of choice for the management of PCOS.

KEY WORDS: ***Polycystic ovary syndrome, Treatment, Side effect, Siddha, Thumattikkai mezhugu, DHEA,FSH***

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1. Introduction

Polycystic ovary syndrome (PCOS) is a complex, common reproductive and endocrine disorder affecting up to 17.8% of reproductive aged women [1]. The common symptoms of PCOS include irregular menstrual cycles, weight gain, subfertility, and infertility [2]. The symptoms also include lack of ovulation, high androgen levels and high numbers of ovarian cysts. Two of the above three parameters are used to diagnose PCOS in women [3]. Approximately three-quarters of PCOS patients have high androgen levels, and this hyperandrogenism is thought to be genetically acquired and an effect of the environment on the hypothalamic-pituitary-ovarian axis [4].

Medical management places strong emphasis on a multidisciplinary approach as pharmaceutical treatments appear to be only moderately effective in treating individual symptoms [5,6]. Conventional pharmaceutical management is limited by the prevalence of contraindications in women with PCOS [7], non-effectiveness in some circumstances [8], side effects [9] and by preferences of women with PCOS for alternatives to pharmaceutical management [10].

The treatment of PCOS depends on its symptoms [11].Weight loss [12],oral contraceptives pills, cyclic progestin,[13] spironolactone, and finasteride are used to improve the symptoms by androgen rise [14].Oral contraceptives can increase the IR, heart, and endocrine-related side effects [15,16] in addition to its positive effects. Metformin also has side effects such as nausea and vomiting, diarrhea, bloating and abdominal pain, loss of appetite and metallic taste, deficiency of vitamin B12, and lactic acidosis [17-20].Complementary medicine is one of the most common treatments for a variety of diseases, including PCOS [21]. The use of complementary medicine has been rising during the last 10 years for about 26%–91% and includes many items such as herbal remedies, reflexology, and acupuncture [22].

The use of herbal medicines and phytonutrients or nutraceuticals continues to expand rapidly across the world with many people now resorting to these products for treatment of various health challenges in different national healthcare settings [23]. This past decade has obviously witnessed a tremendous surge in acceptance and public interest in natural therapies both in developing and developed countries [24], with these herbal remedies being available not only in drug stores, but now also in food stores and supermarkets. It is estimated that up to four billion people (representing 80% of the world's population) living in the developing world rely on herbal medicinal products as a primary source of healthcare and traditional medical practice which involves the use of herbs is viewed as an integral part of the culture in those communities [25,26]. Siddha drug like Thumattikkai mezhugu (TM) indicated for the treatment of PCOS but still now there is no proven documentary evidence revealing its efficacy, hence the main objective of the present study is to evaluate the potential of TM against dehydroepiandrosterone (DHEA) induced PCOS in rat model.

2. Materials and Methods

2.1. Animals

Healthy female adult Wistar albino rats of weighing between 200-220 g were used for the study. The animals were housed in poly propylene cages and were kept in well ventilated with 100% fresh air by air handling unit. A 12 light / dark cycle were maintained. Room temperature was maintained between 22 ¬+ 2o C and relative humidity 50–65%. They were provided with food (Sai feeds, Bangalore, India) and water ad libitum. All the animals were acclimatized to the laboratory for 7 days prior to the start of the study. The experimental protocol was approved by The Institutional Animal Ethics Committee of Sathyabama Institute of science and technology, Chennai, Tamil Nadu, India. IAEC ref no: SU/CLATR/IAEC/XV/162/2020

2.2. Experimental Methodology [27-30]

Animals were checked two weeks for regular cycles by smear test. Adult wistar female rats were randomly divided into four groups of six animals each: Control (group I), PCOS (group II), and experimental groups (group III & IV). The control group rats received sesame (s.c, 0.2 ml) as a solvent. PCOS in rat induced by subcutaneous injection of dehydroepiandrosterone (DHEA) at the dose of 6 mg/100 g body weight, dissolved in 0.2 mL of sesame oil for up to 20 days. After induction, rats displayed several salient features of PCOS including menstrual dysfunction and polycystic ovaries. Induction of PCOS will be ascertained by consistent estrus cycle in rats. PCOS induced experimental rats of groups III and IV

received 200 and 400 mg/kg doses of test drug TM for the period of four weeks. Efficacy of test drug which reverse the cycle back to the normal will be taken as an endpoint.

2.3. Sample Collection [31,32]

At the end of the study, before sacrifice, the animals were fasted for overnight with free access to water. Animals were sacrificed with excess anesthesia. Blood samples were collected from retro orbital and cardiac puncture and then hormone estimation were carried out by using Cobas e411 immuno assay analyzer.

2.4. Histopathology [33]

Ovaries from the experimental rats were dissected out and fixed in 10% buffered neutral formal saline and processed. After fixation, tissues were embedded in paraffin. Fixed tissues were cut at 10 µm and stained with hematoxylin and eosin. The sections were examined under light microscope for histological changes.

3.Results

3.1.Effect of TM on serum hormone level(s)

From the result analysis of the present investigation it was clear that the Weight of ovary sample belongs to group II rats shown progressive increase when compare to group I. Treatment with TM at both the dose level shown pronounced decrease in the weight of the ovaries. From the immunoassay analysis it was predicted that FSH level of group II rats shown significant decrease when compare to control group I. Treatment with TM to group III and IV at the dose of 200 and 400 mg/kg shown promising increase in the level of FSH hormone. LH level haven't shown wide variation between the control and treatment group rats. As shown in Table 1.

Table 1: Effect of TM on serum hormone level(s)

Group	FSH (mIU/ml)	LH (mIU/ml)	Ovary Weight (mgs)
Control	7.25 ± 0.47	6.81 ± 0.14	115 ± 1.86
PCOS	1.75 ± 0.11	6.45 ± 0.10	188.8 ± 1.79
PCOS + 200 mg/kg TM	2.25 ± 0.09	6.23 ± 0.14	163.7 ± 3.49
PCOS + 400 mg/kg TM	3.16 ± 0.12	5.98 ± 0.17	138 ± 4.98

Values are mean ± S.E (n = 6 per group).

3.2. Effect of TM on histopathology of rat ovary

Histopathological analysis of ovary sample belongs to group I showing normal corpus luteum (CL) and Primordial follicles with few mature ovarian follicles with no signs of abnormality. Significant increase the number of follicles at varying stages and corpus luteum with numerous signs of proliferation were observed in sample belongs to group II. Treatment with TM at the dose of 200 and 400 mg/kg has significantly reduced the follicle number further restored the histology of corpus luteum almost similar to that of the normal control rats. As shown in Figure 1.

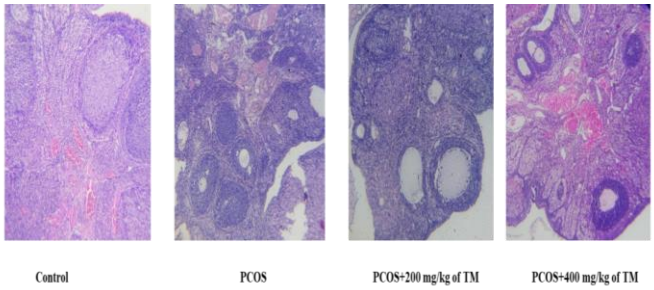

Figure 1: Effect of TM on histopathology of rat ovary

4.Discussion

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women affecting 4-10% of those of reproductive age [34, 35]. PCOS is characterized by hyperandrogenism, insulin insensitivity, and chronic anovulation [36].Research over the last few decades has established that PCOS is an important metabolic disorder. The majority of medicines today contain single active ingredients that are active against a single biological target. Owing to the complexity of the human body, this approach might seem rather simplistic [37]. The scientific viewpoint, in many studies, still reflects reductionist logic. Although it has provided us valuable cellular information, it lacks an overall vision. This approach started to change from the early years of the second millennium. In recent years, a more comprehensive and holistic approach was applied in health-related studies [38]. Traditional medicines of the world often adopt holistic approaches towards human health as well [39]. Unlike conventional drugs, traditional medicine contains medications that are often multicomponent and, therefore, multi-target [40]. In medical practice, one of the areas in which physicians find difficulties in curing patients are syndromes that have a set of signs and symptoms correlated with each other and with a specific disease.

Abnormality of the hypothalamic-pituitary-ovarian or adrenal axis has been imposed in the pathophysiology of polycystic ovarian disease. A disturbance in the secretion pattern of the gonadotrophin-releasing hormone (GnRH) results in the relative increase in LH to FSH release [41]. Ovarian estrogen is responsible for causing an abnormal feedback mechanism that caused an increase in LH release [42]. Usually, in healthy women, the ratio between LH and FSH usually lies between 1 and 2. In polycystic ovary disease women, this ratio becomes reversed, and it might reach as high as 2 or 3 [43].

It was evident from the present investigation that the weight of ovary sample belongs to group II rats shown progressive increase when compare to group I. Treatment with TM at both the dose level shown pronounced decrease in the weight of the ovaries. From the immunoassay analysis it was predicted that FSH level of group II rats shown significant decrease when compare to control group I. Treatment with TM to group III and IV at the dose of 200 and 400 mg/kg shown promising increase in the level of FSH hormone. LH level haven't shown wide variation between the control and treatment group rats

Histopathological analysis of ovary sample belongs to group I showing normal corpus luteum (CL) and Primordial follicles with few mature ovarian follicles with no signs of abnormality. Significant increase the number of follicles at varying stages and corpus luteum with numerous signs of proliferation were observed in sample belongs to group II. Treatment with TM at the dose of 200 and 400 mg/kg has significantly reduced the follicle number further restored the histology of corpus luteum almost similar to that of the normal control rats.

5. Conclusion

The results of the present study reveal that the siddha formulation Thumattikkai mezhugu contributes significantly to the treatment of the PCOS induced by dehydroepiandrosterone . It is clear that drug has positive effects on the ovary and also displaying effects on reversing the FSH, LH and weight of the ovary in the treated rats an important factor in the treatment of PCOS.

Acknowledgement

We wish to acknowledge my thanks to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India and The Noble research solutions, Chennai, Tamil Nadu, India for their support.

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