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Curcumin and Teupolioside attenuate signs and symptoms severity associated to hirsutism in PCOS women: a preliminary pilot study

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Abstract. – OBJECTIVE: Hirsutism affects 5-15% of women of reproductive age, with approximately 80% of these women having polycystic ovary syndrome (PCOS). The etiopathogenesis of PCOS remains unclear, the clinical characteristics of PCOS include hyperandrogenism, generally manifested as hirsutism and acne, and both these clinical symptoms are treated with oral contraceptive pills (OCPs), topical medications or antiandrogens. Curcumin (diferuloylmethane) and Plant sterols, such as a phenylpropanoid glycosides of Ajuga reptans, known as Teupolioside, have attracted considerable attention due to their pharmacological properties. Taking into consideration wide-ranging pharmacological and biological properties and the safety of herbal extracts, we proposed a combination of curcumin and teupolioside to evaluate the anti-androgenic properties in women with PCOS and clinical signs of hyperandrogenism.

PATIENTS AND METHODS: Six hyperandrogenic PCOS women with a hirsutism score (HS) > 20, according to Ferriman-Gallwey scoring system, were involved in the study. These women were treated with a galenical preparation mixture containing curcumin and teupolioside and clinical features were assessed after 12 weeks.

RESULTS: The nutraceutical combination containing curcumin/teopolioside ameliorated clinical manifestations associated to hyperandrogenism in women with PCOS after a 12-weeks treatment.

CONCLUSIONS: This pilot study suggests that a curcumin/teopolioside nutraceutical combination is beneficial for improving various clinical manifestations associated to abnormal hormonal parameters in PCOS women, as well as signs and symptoms associated to hyperandrogenism.

Key Words:
PCOS, Hirsutism, Curcumin, Teopolioside.

Introduction

Hirsutism affects 5-15% of women of reproductive age, with approximately 80% of these women having polycystic ovary syndrome (PCOS)[1,2]. PCOS is the most common endocrine abnormality affecting reproductive age women. Population-based studies estimate a prevalence of 5-10%[3,4]. Features associated with PCOS include physical attributes of hyperandrogenism, such as hirsutism, acne, deepening of the voice, and male pattern baldness; as well as various disorders, such as ovulatory dysfunction, infertility, endometrial hyperplasia, endometrial cancer, mood disorders, obstructive sleep apnea, obesity, insulin resistance, hypertension, hyperlipidemia, and cardiovascular diseases[5,6]. The frequency and degree of expression of these features varies among patients. Although the etiopathogenesis of PCOS remains unclear, the clinical characteristics of PCOS include hyperandrogenism, generally manifested as hirsutism

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and acne, and both these clinical symptoms are treated with similar drug therapies, including oral contraceptive pills (OCPs), topical medications or antiandrogens such as spironolactone, flutamide and finasteride, as well as topical medications[3]. PCOS can be also considered a neuroendocrine syndrome, because both steroidogenesis and folliculogenesis are also dependent upon neurological circiuts[7]. Autonomic deregulation was also observed in PCOS patients compared to healthy subjects[8].

Curcumin (diferuloylmethane), a lipophilic yellow pigment of turmeric with polyphenol agent due to its biological and pharmacological properties including antioxidant and anti-inflammatory features has attracted considerable attention as the most bioactive molecule[9]. It also influences a wide spectrum of diseases; for instance, it has been reported to exert protective effects against cancer, memory decline, Parkinson's disease, atherogenic dyslipidemia, inflammatory disorders, and osteoarthritis[10,11]. There is also evidence for its beneficial hypoglycemic and hypolipidemic effects in different pathological conditions in humans and various experimental models of PCOS[12,13].

Plant sterols or phytosterols (PS) are bioactive components shown to exhibit various pharmacological properties[14]. Being structurally similar (with four rings) to synthetic 5α-reductase inhibitors finasteride and dutasteride, they could stand as the strongest promising candidate for plant-derived 5α-reductase inhibitors. Teupolioside (also known as Lamiuside "A") is a phenylpropanoid glycosides of *Ajuga reptans*, a Mediterranean traditional herbal medicine used for many diseases (e.g. cardiovascular complications, skin disorders, respiratory tract disorders)[15]. Teupolioside represents a natural source of caffeic acid, a phenylpropanoid, and *in vitro* studies have shown that this molecule is able to suppress androgen activity of DHT testosterone by acting primarily on the enzyme 5α-reductase, which can be of interest especially in juvenile acne and in the prevention of hair loss in androgenetic alopecia[16]. However, the potential naturally derived 5α-reductase activity needs to be clinically demonstrated in wider controlled clinical studies. Our proposed mechanism of action shows how the combination of curcumin and teupolioside may counteract hyperandrogenism in PCOS (Figure 1). Specifically, teupolioside acting primarily on the cells of the ovary as 5α-reductase inhibitors results in a reduction of serum levels of dihydrotestosterone (DHT). On the other hand, curcumin has been shown to inhibit androgen receptors (AR) and have antiandrogenic effects[17].

Taking into consideration wide-ranging pharmacological and biological properties and the safety of herbal extracts, we proposed a combination of curcumin and teupolioside to evaluate the anti-androgenic properties in women with PCOS and clinical signs of hyperandrogenism.

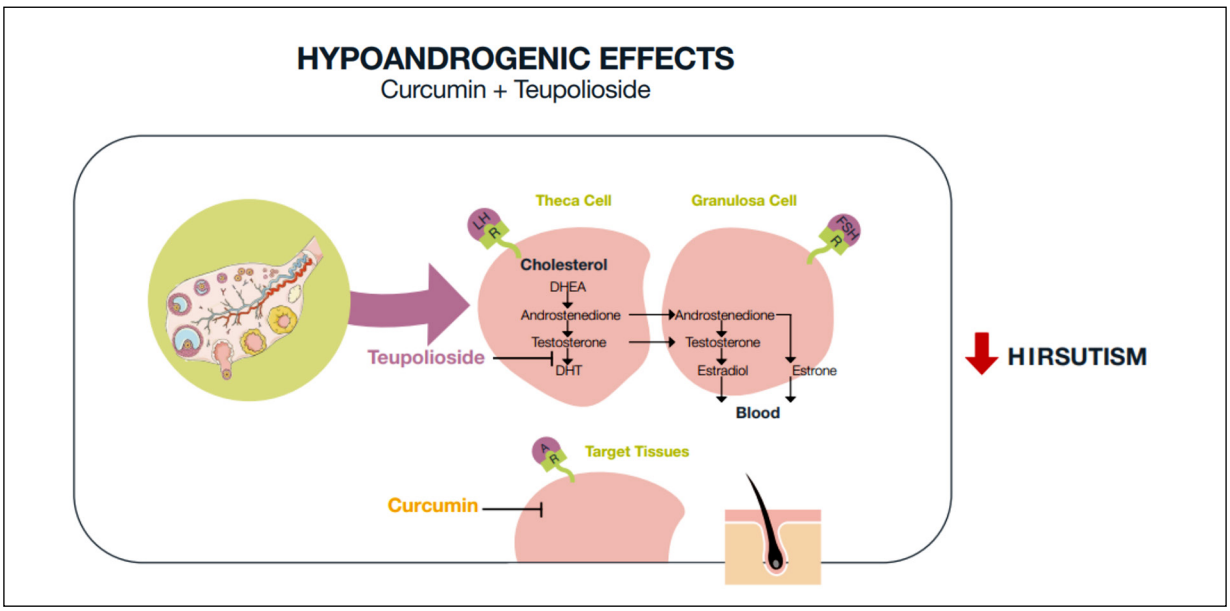

Figure 1. Schematic mechanism of action of curcumin and teupolioside in PCOS and clinical manifestations of hirsutism.

Patients and Methods

Six hyperandrogenic PCOS women, in age range 21-37 years, were followed in the study. All patients had a hirsutism score (HS) > 20, according to Ferriman-Gallwey scoring system[18]; all had menstrual irregularities (oligomenorrhea) and chronic anovulation. Body mass index (BMI) (weight/height^2, expressed as kg/m^2) was recorded at the beginning of the study. The patients had normal glucose tolerance and normal markers of thyroid, liver, and kidney function. None of them had been on oral contraceptives or undergone other hormonal treatments in the 6 months before starting the study, nor any were taking supplements or on a particular diet. Patients were advised to avoid mechanical modifiers, such as shaving, depilation, electrolysis, laser epilation, and creams that slow hair growth, as well as not to change their usual eating habits and physical activities, throughout the treatment period.

Patients were treated with a galenical preparation mixture containing (cps): 250 mg of curcufast (75 mg of curcumin and 175 mg Magnesium dihydroxide, Prolabin&Tefarm), 175 mg of granular curcumin, 35 mg of Teupol, 200 mcg of folic acid, 12.5 mcg of vitamin D, 0.7 mg of vitamin B6. Patients were instructed to take 2 cps a day, one in the morning and one in the evening, preferably on an empty stomach. After 12 weeks patients underwent a routine clinical examination, hirsutism and acne were evaluated as well as the menstrual cycle. Transvaginal ultrasounds were performed to evaluate growing follicles and ovulation.

Acne lesions were scored using to the Global Acne Grading System (GAGS)[19]. This system divides the face, chest, and upper back into 6 areas: the forehead, right cheek, left cheek, nose, chin, and torso (chest and upper back combined). Each acne lesion is described and scored as a comedo (1 point), papule (2 points), pustule (3 points), or nodule (4 points); absence of an acne lesion in an area result in a score of 0 points. The local score for each anatomic area is determined by multiplying the score of the most severe lesion by an area factor (1 to 3), and the local scores of the 6 areas are then added together to obtain the total score. Acne severity is graded as none (total score, 0 points), mild (total score = 1-18 points), moderate (total score = 19-30 points), severe (total score = 31-38 points), and very severe (total score = 38 points). Hirsutism was assessed using a modified Ferriman-Gallwey (FG) score[20], where the hair distribution in 11 androgen-sensitive areas is scored from 0 (none) to 4 (frank virilization). The scores from each area are summed to give the total score, indicating no (0 points), mild (1-7 points), moderate (8-15 points), or severe (more than 15 points) hair growth. Hirsutism was defined by a total FG score of ≥ 8.

Statistical Analysis

Considering 6 PCOS women in this pilot study, $p = 0.05$, and the use of the χ^2 test, the study was estimated to have an 80% power rejection of the null hypothesis that the nutraceutical supplementation does not change the parameters in PCOS women. The power of the study was calculated using PS Power and Sample Size ver. 3.0, 2009. Continuous variables were presented as median values ± standard deviation (SD). Quantitative variables were compared by means of a paired Student's *t*-test baseline *vs.* 12-week treatment. Differences will be considered to be significant for values of $p \leq 0.05$. All calculations were performed using IBM-SPSS® version 22.0 (IBM Corp., Armonk, New York, NY, USA, 2013).

Results

Women were homogeneous regarding mean age, BMI, acne score and HS (Table I). Table II shows changes in hirsutism and acne levels after 12 weeks of treatment, and both resulted in lower values. Interestingly, menstrual regularity was obtained in three out of six patients. Parameters, such as glucose tolerance, thyroid, liver, and kidney function, remained unaltered.

Discussion

It is well known that the etiopathogenesis of PCOS remains poorly understood, and many are the proposed treatment strategies adopted. The treatment options (pharmacological and nutraceutical) for metabolic and hyperan-

Table I. Clinical characteristics at baseline.

Characteristics	Mean ± SD
Age (y)	24.5 ± 3.3
BMI (kg/m^2)	22.05 ± 2.1
Hirsutism (Ferriman-Gallwey score)	22.6 ± 2.90

Table II. Variation of clinical characteristics after 12 weeks.

	Baseline	12 weeks
BMI (kg/m^2)	22.05 ± 2.1	22.32 ± 2.2
Hirsutism (Ferriman-Gallwey score)	22.6 ± 2.90	12.2 ± 6.43
Acne (GAGS score)	19.5 ± 9.2	8.5 ± 5.2
Menstrual irregularity	6/6	3/6

drogenic alterations in PCOS include inositol, metformin, vitamin D and α-lipoic acid. Among them, insulin-sensitizer agents, such as metformin and inositol-based supplements, are the most widely used. Generally, these supplements are based on myo-inositol (myo), D-chiroinositol (DCI) or a combination of both. The biological activity of inositols is mainly due to their ability to increase insulin sensitivity by acting on insulin signaling pathway, playing a pivotal role in PCOS physiopatology[21,22]. At the clinical level, DCI supplementation has also been shown to regulate the menstrual cycle and testosterone levels[23,24]. Very often, these molecules are also associated with other compounds, such as α-lipoic acids[25], melatonin[26] and vitamin D[27] in order to enforce their biological activity on the metabolic aspect of PCOS. Considering that, up to date no dietary supplements strictly focus on the modulation of androgenic aspects of PCOS by primarily on the metabolic syndrome. Thus, this novel formulation based on curcumin and teupolioside is positioned as a targeted and specific treatment for the management of the androgenetic aspects of PCOS, and it could be of a great interest.

Limitations

Our pilot trial had a small sample size that makes it difficult to detect small changes due to curcumin/teopolioside treatment. Our research was also limited to selected clinical parameters and we were not able to measure other endocrinological or metabolic parameters. Investigating the effects of curcumin and teopolioside on reproductive hormones, including androgen levels and also sex hormone-binding globulin (SHBG), would be of great value. Also, the quantification of serum or plasma curcumin levels still needs to be further investigated., Although the conclusions of this study show that curcumin/teopolioside supplementation might be beneficial for improving various clinical manifestations associated to abnormal hormonal parameters in PCOS women, as well as signs and symptoms associated to hyperandrogenism, future trials with larger scales and duration to support the findings are warranted.

Conclusions

Overall, this pilot study suggests that a curcumin/teupolioside nutraceutical combination ameliorates clinical manifestations associated to hyperandrogenism in women with PCOS. The 12-weeks treatment showed promising results on many clinical manifestations of hirsutism, such as menstrual irregularity, hirsutism, acne and autonomic features. Only further studies can analyze the long-term clinical benefits of use of this combination in women with PCOS and its effects on biochemical levels of hyperandrogenism, and not only the clinical signs.

Therapeutic decisions in PCOS depend on the patients' phenotype and should focus on regulating androgen excess, improving metabolic status and improving fertility[19]. In this regard, a treatment with a curcumin/teopolioside combination could lead to better results.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

All patients recruited for the study were fully counseled and signed a written informed consent.

Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of international research committee.

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