Review Article

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Polyphenols in Polycystic Ovary Syndrome: A Perspective

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Abstract

Polycystic ovary syndrome is one of the most common hormonal endocrine disorders that affects around 5-10 percent women of childbearing age and is characterized by abnormal hormone levels. Natural polyphenolic compounds found in plants known as flavonoids (catechins) and non-flavonoids (resveratrol, chlorogenic acids) have recently become very popular. This review article is an attempt to present the findings of scientific studies with regard to beneficial effects of polyphenols on humans affected by pcos. Relevant Papers were identified from Science Direct, Google Scholar and pubmed by using all combinations of the search terms related to polyphenol and pcos.

Keywords: Polycystic Ovary Syndrome; Polyphenol; Resveratrol; Catechins; Chlorogenic Acids.

Introduction

The female body is equipped with the power to create new life out of just a few microscopic cells. But along with that comes many physical burdens. Polycystic ovary syndrome (PCOS) is the most common hormonal condition in women across the globe.The three most common features of PCOS include irregular periods, excess androgen in the body,and polycystic ovaries that become enlarged and contain many fluid sacs.Women with pcos produce marginally higher amounts of testosterone and other male hormones than average[1]. There is evidence suggesting that elevation of these hormones contribute to infertility, weight gain, acne or excess body hair, associated [2] with other health issues as illustrated in Table1.

Table 1: Signs and Symptoms

• Hyperandrogenism
• Increased sympathetic nerve activity
• Altered GH/IGF-1 axis
• Hypersecretion of LH
• Anovulation
• Visceral obesity
• Hypertension
• Insulin resistance
• Psychological stress
• LH, Luteinising hormone;
• GH, growth hormone;
• IGF, insulin growth factor

Raja-Khan N et al [3] addressed other risk factors to aggravate this condition: insulin resistance, obesity, hypertension, dyslipidemia, inflammation and subclinical cardiovascular disease. Anxiety, depression and reduced quality of life are also common. Pcos is characterized by lipidic blood profile, bigger adipocytes and insulin resistance. Studies performed on monkeys, sheep and rats demonstrate that prenatal androgenization is a cause of pcos [4]. In human, only one study has verified the presence of testosterone in the blood of babies from PCOS mothers [5].

Evidence suggests that vitamin D deficiency may be a causal factor in the pathogenesis of IR and the metabolic syndrome in pcos [6].

Research suggest [7] that the theca interstitial cells of the ovary are responsible for producing male hormones which are normally required for healthy ovarian function. However in pcos, the large amount of these cells causes a large amount of male hormones

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to be produced, causing problems with normal ovulation.This often results in delay in ovulation (and therefore in menstruation) or lack of ovulatory cycling altogether in more severe cases.These hormonal changes also greatly reduce egg quality and health.The two causes for the excessive overgrowth of these theca interstitial cells of the ovary are:

1. High levels of oxidative stress and
2. High levels of insulin in the local tissues.

Both these factors play a great role in the pathology of polycystic ovarian syndrome. Because pcos is a multifactorial pathology several treatments (Table 2) have been proposed [8].

Table 2: Therapeutic tools in the treatment of Pcos

1.	**Old Therapy** Oral contraceptives (OC) Anti-androgens
2.	**New Therapy** Insulin sensitizers: *(Metformin Thiazolinediones)*
3.	**Emerging Therapy** Statins Acupuncture Dietary products and nutrients. Vitamin D Herbal medicines Vitamin B12 and folate. Resveratrol AGEs low diet (atherogenic and endogenous) Phisical activity

Polyphenols in Pcos

Natural polyphenolic compounds found in plants known as flavonoids (catechins) and non-flavonoids (resveratrol, chlorogenic acids) have recently become very popular. There is evidence[9] suggesting that resveratrol, a natural plant polyphenol found in grapes, berries, and medicinal plants,which is sought after by nutritionists and biochemists for its potential anti-cancer,anti-oxidant and anti-inflammatory property ,is now proved to lower levels of testosterone in pcos women. It balances lipid profile, decreases adiposity and improves insulin sensitivity. Tomatis. V et al [10] opines that Green tea (catechins, GTC) and coffee polyphenols (chlorogenic acids, CGA) have been associated with reduced diabetes and cardiovascular risk in Women with Polycystic Ovary Syndrome. Quercetin, derived from Chinese medicinal herbs such as hawthorn, has proved practical in the management of insulin resistance (IR)in women with polycystic ovary syndrome [11].

Resveratrol and other polyphenols (flavanols, flavonoids, anthocyanins and phytochemicals) are produced as part of the plant's defense system against infection [12]. The compound is found throughout the plant: in the vines, roots, seeds and stalks, but the highest concentration of resveratrol is in the grape skin. Some other rich plant sources of resveratrol include eucalyptus, spruce and lily, peanuts and berries of all forms (including blueberries, huckleberries and cranberries[13]. Content of resveratrol in grapes varies from 0.16 to 3.54 μg/g; dry grape skin contains about 24 μg/g of resveratrol. Resveratrol is also present in other berries and nuts. For example, cranberry raw juice contains about 0.2 mg/L. In other natural foods, the concentration of resveratrol varies in the range of μg/g (peanuts, pistachios) to ng/g (bilberries, blueberries) . It has been documented that red wine contains a much greater amount of polyphenolic compounds than white wine. The concentration of resveratrol ranges from 0.1 to 14.3 mg/L in various types of red wine, while white wines contain only about 0.1–2.1 mg/L of resveratrol [14].

Dr. Bill Rawls a gynecologist practicing conventional medicine for over 20 years suggest Japanese knotweed as an excellent source of resveratrol, Once planted, the rhizome (root) expands rapidly, pushing out any other plants in the vicinity.

Bioavailability

Low solubility of resveratrol in water (<0.05 mg/mL), caused by its chemical structure, affects its absorption . In animals and humans, resveratrol is quickly metabolized in liver; in plasma it binds to lipoproteins and albumin, and this facilitates its entry to cells [15]. Resveratrol (Figure 1) presents itself in both *trans*- and *cis*- isomeric forms [16].

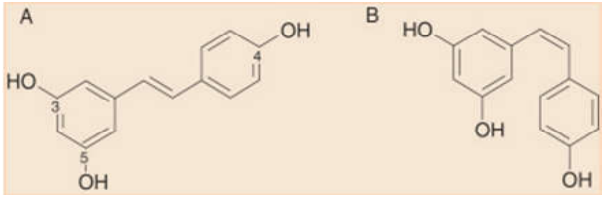

Fig. 1: Chemical structure of *trans*- (A) and *cis*-resveratrol (B).

The absorption and metabolism of resveratrol appears to be broadly similar to that of other polyphenols such as quercetin and catechin, although a number of factors may influence the pharmaco-kinetics of each.

Oxidative Stress and Inflammation

Resveratrol has been reported by Ketan RP [17] to decrease oxidative stress and attenuate inflammation, and these mechanisms may account for its health

benefits in pcos. Oxidative stress occurs when an excess of reactive oxygen species (ROS) are generated from any of a variety of sources, including the mitochondrial electron transport chain and reduced nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidases. ROS can damage macromolecules and activate signaling pathways that include a number of inflammatory mediators . Inflammation, in turn, can lead to further oxidative stress in a cycle that contributes to the progression of many diseases. Current evidence of actions of resveratrol on the ovary in rat models by Wong et al [18] sugests that.

1. Invitro- resveratrol inhibits proliferation and androgen production by theca-interstitial cells. Resveratrol also exerts a cytostatic, but not cytotoxic, effect on granulosa cells, while decreasing aromatization and vascular endothelial growth factor expression.
2. In vivo- resveratrol treatment reduces the size of adipocytes and improves estrus cyclicity in the previously acyclic rat model of polycystic ovary syndrome (PCOS).

PCOS- Common Endocrine Disorder of Reproductive-Age Women

Some interesting findings of resveratrol on women with PCOS were reported in the journal of clinical endocrinology and metabolism from the study conducted by Beata Bet al[19] at the Poznan University of Medical Sciences in Poznan,Poland.The first randomized, double-blind, placebo-controlled clinical trial recruited a total of 30 women with PCOS randomly to two groups. They were treated daily with either 1,500 milligrams of resveratrol or placebo for 3 months to determine levels of testosterone and other androgen hormones.The study cited that resveratrol significantly reduced ovarian and adrenal androgen. The polyphenol called a phytoalexin was found to lower the levels of testosterone and dehydroepiandrosterone sulfate (DHEAS), another hormone that the body can convert into testosterone in pcos patients. The study also stated the effect to be, at least in part, related to an improvement of insulin sensitivity and a decline of insulin level. Finaly the study concluded that resveratrol (1,500 mg/day) significantly reduces total serum testosterone and DHEAS in women with polycystic ovary syndrome.

A study published in Science Daily - 2016 [20] has given a new insight into why some women have difficulty falling pregnant.Led by the research team Dr Simon Lane a research fellow at the University of Southampton involved taking immature mouse eggs and incubating them in follicular fluid taken from women who have endometriosis, in vitro. The researchers examined the amounts of ROS (Reactive Oxygen Species) that were generated and the ability of the egg to mature. They found the follicular fluid from women with endometriosis resulted in higher amounts of ROS and the ability of the egg to mature was blocked by endometriosis, Resveratrol when added to the follicular fluid taken from women who have endometriosis found ROS levels decreased and more eggs were able to mature.

In a 16-week, single-blind, unilateral crossover trial, by Tomatis V et al [21] on effects of green tea (catechins, GTC) and coffee polyphenols (chlorogenic acids, CGA) that recruited 12 PCOS women (mean ± SD: age, 28 ± 10 y; BMI, 35 ± 7 kg/m^2; fasting insulin, 97 ± 52 pmol/L) who underwent 8 weeks of placebo treatment followed by 8 weeks of active treatment (tablets providing 2093 mg GTC and 220 mg CGA/day) found a reduced waist circumference (MD:2.4cm; P = 0.02), altered eicosanoid profile. It is postulated that a combined intake of GTC and CGA may modulate eicosanoid pathways, thereby reducing inflammation and abdominal adiposity.

Insulin resistance (IR) is a clinical feature of polycystic ovary syndrome (PCOS). Wang Z et al [22] demonstrated that quercetin, derived from Chinese medicinal herbs such as hawthorn,decreases insulin resistance in a polycystic ovary syndrome rat model by improving inflammatory microenvironment. The underlying mechanism of quercetin potentially involves the inhibition of the Toll-like receptor/NF-êB signaling pathway and the improvement in the inflammatory microenvironment of the ovarian tissue of the pcos rat model.

Brown adipose tissue has been a recent target for obesity prevention and therapy. Srujana R.et al investigated the novel mechanism through which a well-studied anti-obesity phytochemical resveratrol (RSV) induced browning of white adipose tissue (WAT). The study suggest that RSV-induces change in the polarity of macrophages leading to elevated levels of catecholamines that will induce browning of WAT and contributes to the anti-obesity effects of RSV.

Study by Hossein KJ et al [24] on the effect of pomegranate extract on hormonal changes caused by polycystic ovary syndrome in female wistar rats revealed that the phenolic compounds of pomegranate extract lead to reduced effect of testosterone hormone through inhabitation from formation of dihydrotestosterone receptor complex, reduce secretion of testosterone hormone and increased concentration of oestrogen in wistar rats.

Resveratrol came to scientific attention as one part of a possible explanation for the french paradox – the low incidence of obesity and heart disease among french people who eat a relatively high-fat diet. A key factor attributed to this was the French custom of drinking wine with meals. The health benefits of red wine consumption have been attributed to polyphenols; resveratrol, found in high concentrations in red wine, is a major constituent of polyphenols [25].

How does all of this relate to Ayurveda? Thousands of years ago the rishis (sages) with their power of pratyeksha (direct perception) put together herbal super-formulas made with a synergetic blend of numerous fruits and herbs. Two of these are known as chyavanprash and darakchasava. Rammohan Rao a graduate of the California College of ayurveda opines that these tonics were designed to nourish the body and mind, promote longevity and support strong immune system function. These polyphenols promote free radical scavenging, protection by antioxidants, reducesLDL cholesterol levels, reproductive abnormalities, especially anovulation and there by impove womens health [26].

Conclusion

There is increasing interest in the dietary components of food and the possible benefits of polyphenolic compounds in women with pcos . Several studies confirm that these compounds have anti-androgenic properties and inhibitory effect on formation of dihydrotestosterone receptor complex. They also reduce secretion of testosterone hormone . These positive results have been shown also in animal models, and their combinations, in clinical applications. Natural polyphenols, may have positive metabolic effects. The road to good reproductive health and extended lifespan also exists in a glass of fruit juice, fruit extract, whole fruits, green leaves, nuts and seeds, all of which contains polyphenols and their derivatives .

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