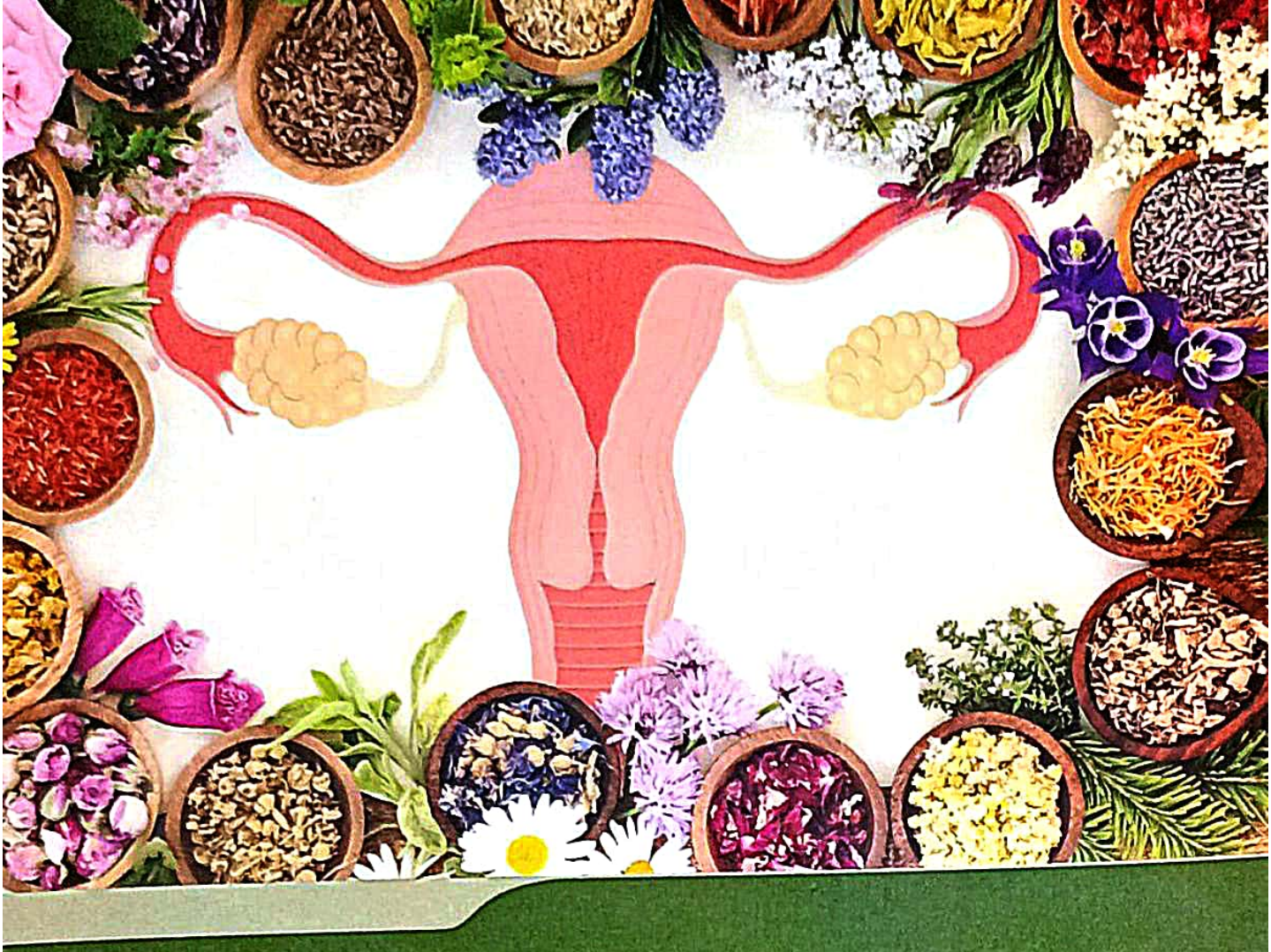


Herbal Medicine Applications for Polycystic Ovarian Syndrome

Edited by
Younis Ahmad Hajam
Rajesh Kumar
D. R. Thakur
and Seema Rai

CRC Press
Taylor & Francis Group

Designed cover image: © Shutterstock

First edition published 2024
by CRC Press
2385 NW Executive Center Drive, Suite 320, Boca Raton FL 33431

and by CRC Press
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

CRC Press is an imprint of Taylor & Francis Group, LLC

ISBN: 9781032383767 (hbk)
ISBN: 9781032383712 (pbk)
ISBN: 9781003344728 (ebk)

DOI: 10.1201/9781003344728

Typeset in Times
by codeMantra

Contents

3 Potential Phytotherapeutic Intervention for the Treatment of Polycystic Ovarian Syndrome

Seema Rai, Sushmita Pal, Adyasha Purohit, Sunita Patel, Kshipra Xaxa, and Gunja Roy
Guru Ghasidas Vishwavidyalaya

Younis Hajam Ahmad
Sant Baba Bhag Singh University

Rajesh Kumar
Himachal Pradesh University

CONTENTS

DOI: 10.1201/9781003344728-3

3.1 INTRODUCTION

Nowadays, the most common ovarian disorder is polycystic ovarian syndrome or PCOS. It was first discovered by Stein and Leventhal in 1935 (Leventhal and Cohen, 1951). Hence, it is referred to as Stein–Leventhal syndrome (Leventhal, 1958). It is one of the most common endocrine and metabolic disorders in which the women ovaries produce immature or partially mature eggs in large quantities and develop into ovarian cysts. It occurs mainly in 2%–20% of the reproductive age group (Knochenhauer et al., 1998; Rai et al., 2015; Basheer et al., 2018). Nowadays, the PCOS has become a severe issue.

PCOS is a type of secondary amenorrhea (Leventhal, 1958), which includes irregular menstruation or amenorrhea, i.e., absence of menstruation. FSH is responsible for follicular maturation and ovulation. Lack of FSH arrested the growth of antral follicles which causes irregular cycles and anovulation in PCOS women (Doi et al., 2005). Type 2 diabetes, hyperinsulinemia, and glucose intolerance are the metabolic symptoms (Tasali et al., 2008). Physical signs are hirsutism (excessive hair growth on the face), alopecia, overweight, acne, inappropriate male features, oily skin, etc. It occurs in the beginning of adolescence (Teede et al., 2010). Women with PCOS have higher chances of coronary artery diseases and stroke due to high level of LDL cholesterol and low level of HDL (Macut et al., 2013). Hyperandrogenism or male-like features, insulin resistance, and ovulatory dysfunction are the major indications in women with PCOS (Jahan et al., 2018). Women with PCOS exhibit comparatively high emotional distress such as anxiety, depression, poor self-esteem, and reduced quality of life (Coffey et al., 2006; Tasali et al., 2008; Benson et al., 2009; Veltman-Verhulst et al., 2012). Obstructive sleep apnea is also a determinant factor in women with PCOS (Tasali et al., 2008).

Dyslipidemia is a common risk factor in women with PCOS. It has been suggested that dyslipidemia, obesity, and hyperinsulinemia may be responsible for PCOS-related oxidative stress. Due to the presence of excessive adipose tissue and overproduction of reactive oxygen species (ROS) the oxidative stress seems to be increased in women with PCOS. Overproduction of ROS is responsible for the high level of free radicles, such as superoxide radicles and hydrogen peroxide in mitochondria (Macut et al., 2013; Sharma et al., 2022).

Low levels of sex hormone binding globulin (SHBG) leads to hyperandrogenemia (Qu and Donnelly, 2020). Increasing oxidative stress leads to an increase in number of cardiovascular diseases in women with PCOS. According to Das and his coworkers, granulosa cell proliferation in women with PCOS is greater than granulosa cell death or apoptosis (Das et al., 2008). Hence, more granulosa cells produce more estrogen in response to FSH stimulation than normal granulosa cells (Erickson et al., 1990). In women with PCOS, antimullerian hormone (AMH) also presents a high-level output by granulosa cell from preantral and small antral follicles which causes disruptive activity of granulosa cells in women with PCOS (Pigny et al., 2003; Pellatt et al., 2007).

In this chapter, we are starting to explore the effects of resveratrol, quercetin, and 6-gingerol on PCOS.

3.2 PCOS AND REPRODUCTIVE IMPAIRMENTS

Rotterdam reported that women with PCOS have higher level of circulating androgen. The aromatase enzyme primarily converts testosterone and androstenedione into estradiol and estrone throughout the steroidogenesis process (Rotterdam, 2003). However, when problems arise with this enzyme, it causes an increase in ovarian androgen production and development of PCOS (Kafali et al., 2004). In women, androgen is mainly produced from the ovary and adrenal glands. In women with PCOS, the ovaries produce up to 60% of androgen and the adrenal gland produces the remaining 40% (Cedars et al., 1992). This excess production of androgen leads to hyperandrogenism. According to Sterling, in normal women without PCOS, the LH and FSH ratio is 5:20 IU/mL, but in women with PCOS, the LH level increases up to 18 IU/ml and the FSH level decreases up to 6 IU/mL. This change can prevent ovulation well and leads to lower pregnancy and higher miscarriage rate. During the early stage of life, LH and FSH are in equal amounts, but 24 hours before ovulation, the LH level increases up to 25–40 IU/mL. After ovulation, the LH levels decreases (Krishnan and Muthusami, 2017). Women with PCOS have an increased risk of impaired glucose tolerance (Rotterdam, 2003). In normal women, the insulin level is 6–15 μIU/mL, but in women with PCOS, the insulin level increases up to 22 μIU/mL (Joshi et al., 2014; Krishnan and Muthusami, 2017), which leads to hyperinsulinemia and causes diabetes mellitus. Women with PCOS also have an elevated level of dehydroepiandrosterone (DHEAS) (Rotterdam, 2004). In women with PCOS, the high

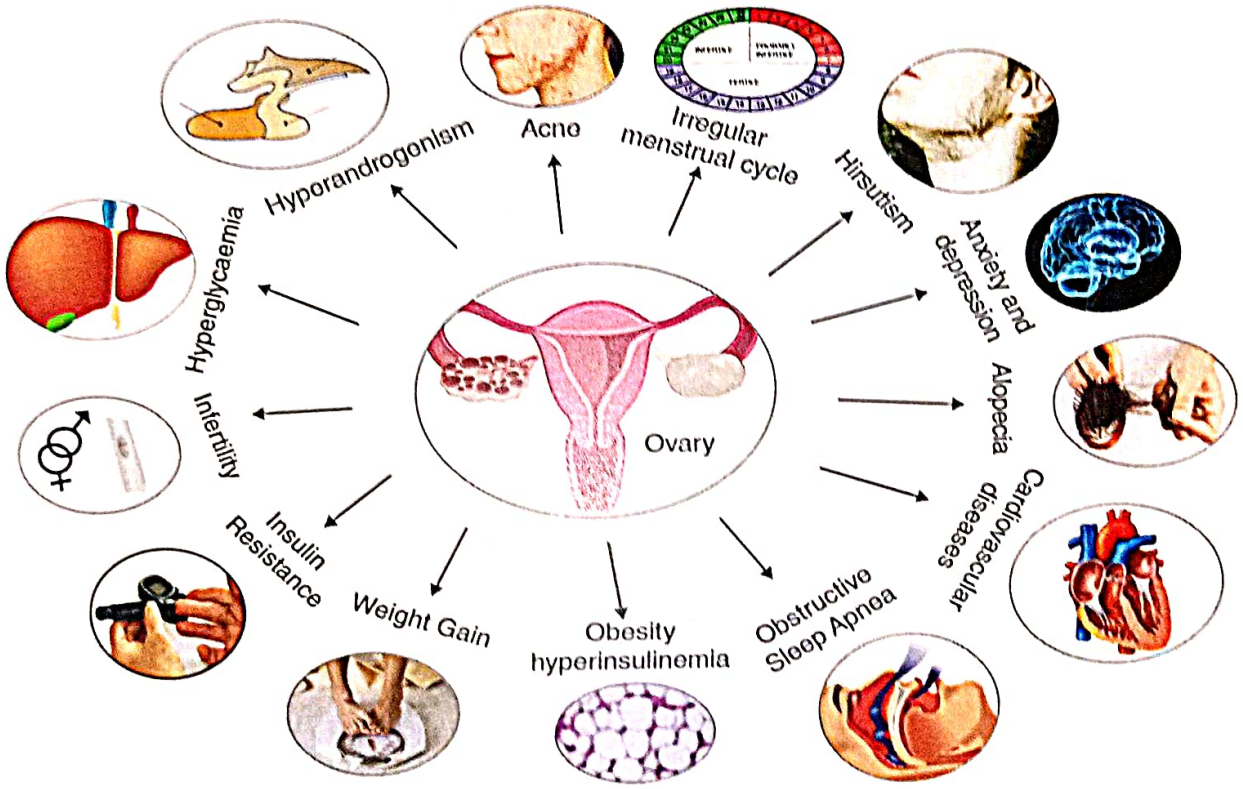


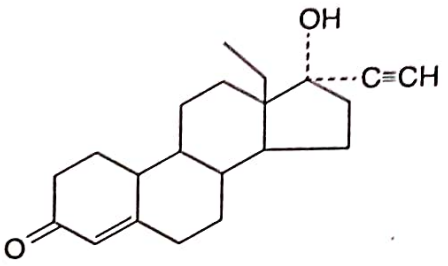
FIGURE 3.1 Various physiological impairments involved in PCOS.

level of insulin may bind with the insulin receptor in the osteoblast cell and reduce bone formation (Krishnan and Muthusami, 2017) (Figure 3.1).

3.3 THERAPEUTIC DRUGS IN PCOS

To date, there are several medications that exist for the treatment of PCOS. For patients with PCOS, medical managements such as oral contraceptive pills, metformin, and hormone therapy were introduced (Mihanfar et al., 2021a).

3.3.1 Oral Contraceptive Pill

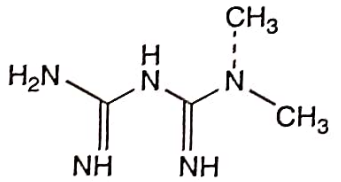


Levonorgestrel

Oral contraceptive pills reduce hyperandrogenism and regulate menstrual cycle by suppressing ovulation and preventing cyst formation (Piparva and Buch 2011; Mihanfar et al., 2021). Research evidence suggests a lot of medications for the treatment of PCOS. However, few studies in the literature suggest cardiovascular and breast cancer as side effects of oral contraceptives.

Furthermore, there are various allopathic drugs in allopathic medicine to treat PCOS.

3.3.1.1 Metformin



Metformin

Brand: Fortamet, Actoplus met, Janumet, Glycon.

Mechanism of action: Previous researchers reported that metformin is primarily used for the treatment of type 2 diabetes and acts as insulin sensitizers. Morley and his coworkers also reported that metformin decreases weight, also decreases the androgen level in blood serum, and improves menstrual irregularities and ovulation (Morley et al., 2017) (Figure 3.2).

3.3.1.1.1 Side Effects of Metformin

They all have many sides effects which are evidenced by the use of these drugs in PCOS treatment. Metformin as a PCOS drug causes other diseases such as gastrointestinal disturbance, lactic acidosis, and renal insufficiency (Jahan et al., 2018).

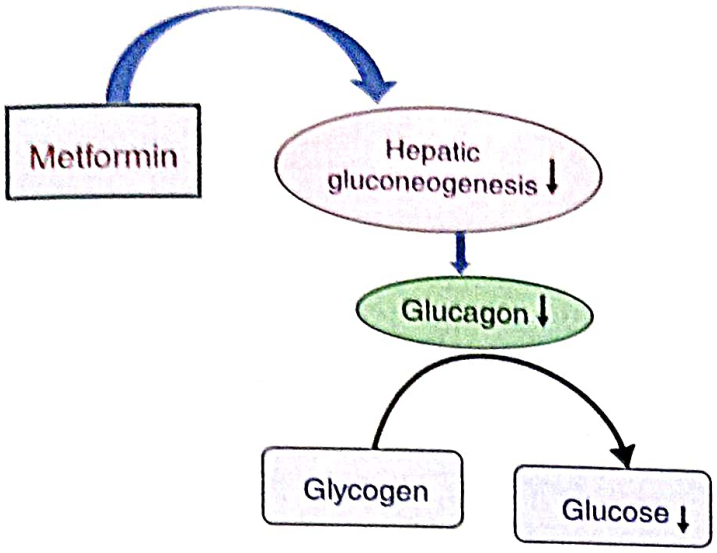
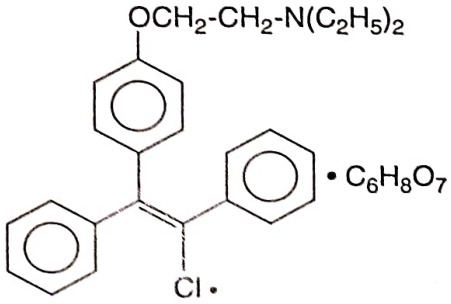


FIGURE 3.2 Schematic flowchart of mechanism of action of metformin. Metformin decreases hepatic gluconeogenesis by inhibiting mitochondrial complexes which have downstream effects on cAMP and protein kinase signaling pathways. As a result, glucagon action decreases and circulating insulin and glucose level on ovaries.

3.3.1.2 Clomiphene Citrate

It has been reported that clomiphene citrate is an estrogen antagonist and is used for the improvement of ovulation in infertile PCOS women (Macgregor et al., 1968). Rosenfield and Ehrmann (2016) also reported that hyperandrogenism is also treated by clomiphene citrate, thereby reducing hyperinsulinemia because hyperandrogenism is the main factor for hyperinsulinemia (Figure 3.3).



Clomiphene citrate

3.3.1.2.1 Side Effects of Clomiphene Citrate

Congenital abnormalities, such as liver diseases, decrease the quantity and quality of cervical mucus, leads to abnormal development or dysfunction of endometrium (Sereepapong et al., 2000; Sovino et al., 2002), and also leads to mood swings, irritability, and feeling down (Choi et al., 2005) (Figure 3.4).

Therefore, clomiphene citrate may not be a suitable drug of choice for long-term PCOS medication (Jahan et al., 2018). Therefore, to treat PCOS, some phytotherapeutic folk medicines need to be explored, as they have been investigated from time to time.

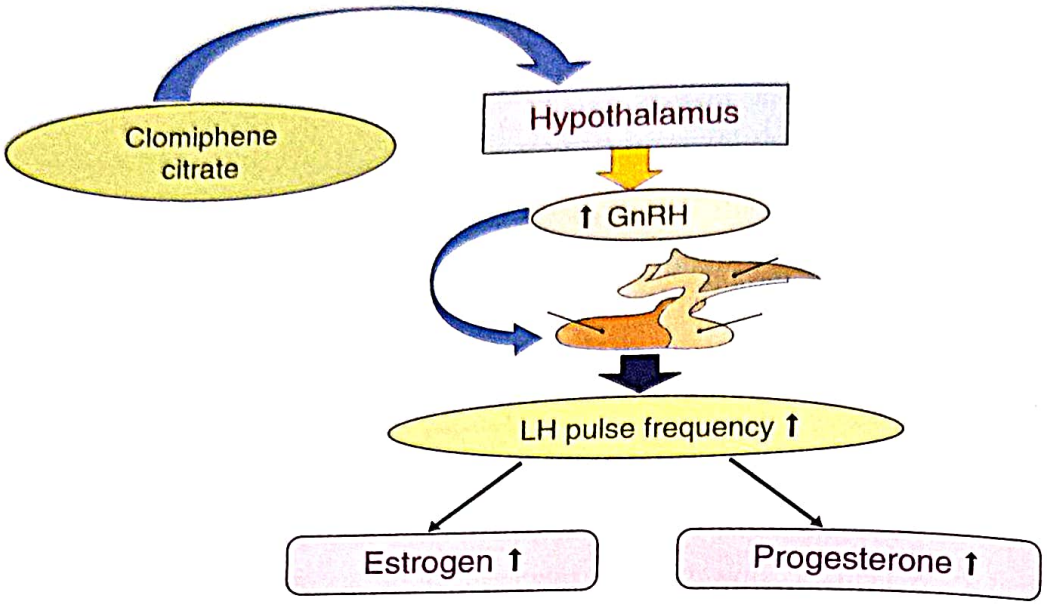


FIGURE 3.3 Schematic flowchart of the mechanism of action of clomiphene citrate. Clomiphene citrate can increase the LH pulse frequency by increasing the pulsatile secretion of GnRH in hypothalamus, thereby increasing the estrogen level before ovulation and the progesterone level during luteal phase.

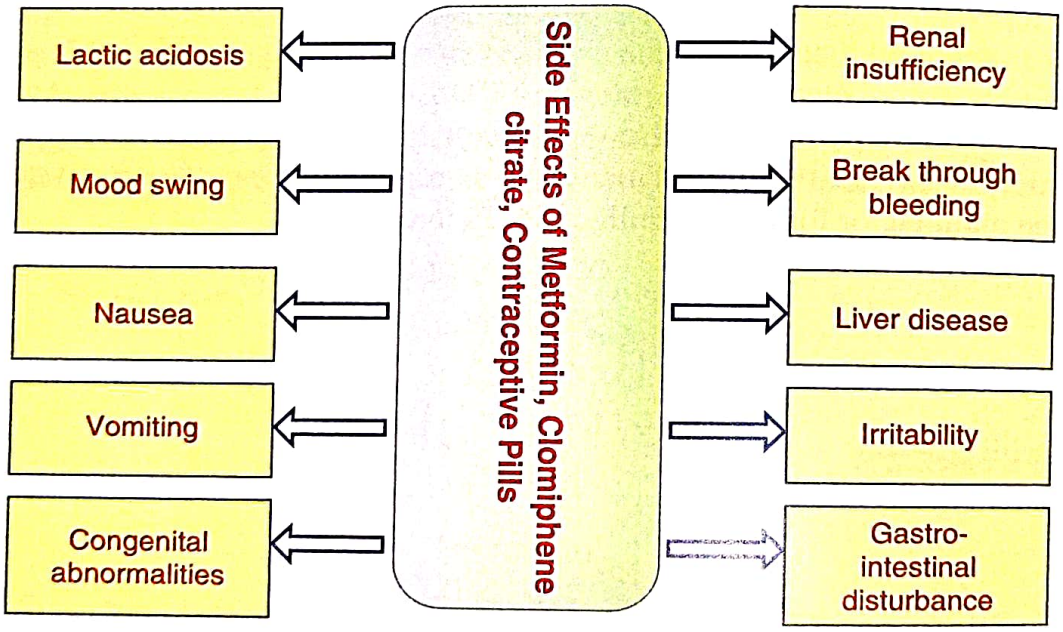


FIGURE 3.4 Schematic diagram showing side effects by using therapeutic medications in PCOS.

3.4 PHYTOTHERAPEUTIC INTERVENTIONS IN PCOS

The present scenario, which is related to the various side effects of the therapeutic drugs, such as metformin, clomiphene citrate, contraceptive pills, and so on, inclined the attention of various researchers toward the nutraceuticals/phytoextracts which contain various polyphenols and bioactive compounds for the treatment of PCOS pathogenicity.

Since ancient times, most of the tribal population use the neutral folk medicine for the treatment of various kind of diseases, including viral infection, inflammation, wound healing, and reproductive disfunction/disorders. In this study, we wish to explore a few plant extracts, such as polyphenols and bioactive compounds, which are widely used to treat PCOS. However, various reports suggest that they are known to have the ability to interfere with different kinds of diseases. It is believed that the phenolic substances from medicinal plants, fruits, and vegetables in diet may play an important role in the protection. Plant polyphenols are dietary antioxidants and act as structural polymers and defense response chemicals (Lin et al., 2016; Rani et al., 2022).

These phytotherapeutic drug could be flavonoid and nonflavonoid compounds. The present study explains about one specific flavonoid, i.e., quercetin and nonflavonoids such as 6-gingerol; another phytomolecule which we have considered is the natural polyphenol is in stilbene family, known as resveratrol (Figure 3.5).

3.4.1 Quercetin

Flavonoids (i.e., quercetin) are hydrophilic natural glycosides which are present in many plants and foodstuffs (Formica and Regelson, 1995). The most common flavonoids are quercetin and Rutin. Quercetin, the chemical name-3,5,7,3′,4′-pentahydroxyflavone, is one of the most common flavanols which is commonly found in fruits and vegetables such as tomato, onion, broccoli, lettuce, grapes, apples, and

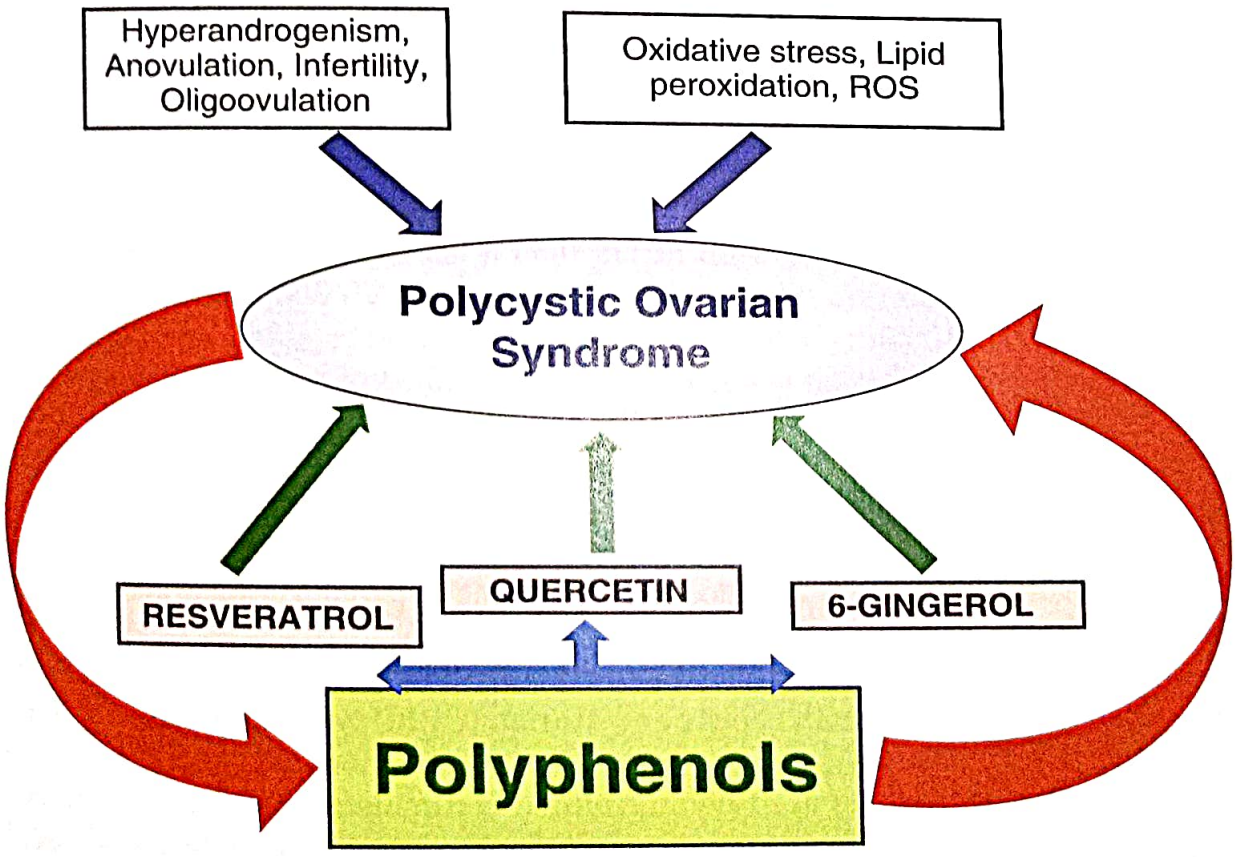
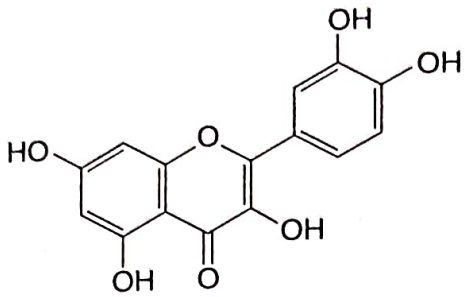


FIGURE 3.5 Polyphenols in PCOS.

blueberries. It was first described by Szent Gyorgyi in 1936 (Formica and Regelson, 1995). It is a nonsteroidal compound and has antioxidant properties.



Structure of quercetin

The present study is based on the effect of quercetin in PCOS. In addition to benefits in PCOS, quercetin exhibits cardiovascular protection, anticancer activity, antidiabatic, anti-inflammatory effect, etc.

3.4.1.1 Quercetin as Phytotherapeutics

Quercetin is a potent therapeutic component (Mihanfar et al., 2021a). The metabolic sensors, AMPK and SIRT-1, play an important role in lipid and adipokines metabolism, glycolysis, and oxidative stress but their expression level decreases in PCOS ovarian tissue (Ruderman et al., 2010; Furat Rencber et al., 2018; Tao et al., 2019; Nejabati et al., 2020). Quercetin plays a regulatory role in AMPK and SIRT-1 activation (Iside et al., 2020). Quercetin supplement increases AMPK and SIRT-1 expression as well as increases insulin sensitivity and lipid and adipokines metabolism (Mihanfar et al., 2021b), thereby improving GLUT4 regulation and glycolysis (Pourteymour Fard Tabrizi et al., 2020). Treatment with quercetin in PCOS improves different biochemical and hormonal parameters as well as ovarian histological parameters (Mihanfar et al., 2021a). The granulosa and thecal layer of secondary follicles are thicker in women with PCOS than a healthy woman. However, quercetin supplement decreases this thickness of granulosa cell and layer of secondary follicle (Jahan et al., 2018). Jahan and his associates also reported that large-sized cystic follicles are created in women with PCOS instead of secondary and tertiary follicles. These cystic follicles were formed due to excess androgen and disrupted folliculogenesis (Wang et al., 2012, Linares et al., 2013). However, quercetin administration decreases this cystic follicle diameter and increases the number of primordial germ cell and primary follicles (Jahan et al., 2018), thereby normalizing the ovarian size and hormonal imbalance and improving hyperandrogenemia (Shah and Patel, 2016).

Insulin stimulates ovarian steroidogenesis by inhibiting hepatic SHBG synthesis (Plymate et al., 1988) and both hepatic and ovarian IGFBP synthesis (Poretsky et al., 1996), which regulates the ovarian growth and cyst formation and alters the adrenal steroidogenesis (Poretsky et al., 1999). Insulin also stimulates the ovarian steroidogenesis by binding to its own receptor and IGF1 receptor on granulosa and thecal

cells of the ovary (Poretsky et al., 1999), which finally leads to the formation of hyperandrogenism and hyperinsulinemia and causes obesity in women with PCOS (Gambineri et al., 2002). However, treatment with quercetin reduces CYP17A1 mRNA expression to prevent excess production of steroidogenic hormones and also decreases ovarian cyst and its weight which finally improves hyperandrogenemia (Shah and Patel, 2016). Quercetin also decreases the total cholesterol level and increases HDL cholesterol (Jeong et al., 2012).

In women with PCOS, the blood-glucose level is high due to high activity rate of α-glucosidase enzyme which breaks down the starch and disaccharides to glucose and causes hyperglycemic condition. However, quercetin inhibits the activity of α-glucosidase, which reduces the blood-glucose level (Shikawa et al., 2007; Kim et al., 2011; Jeong et al., 2012).

A woman with PCOS exhibits excess level of ROS and free radicals, and a decline in the level of antioxidants causes oxidative stress (Maritim et al., 2003). However, quercetin increases the function of antioxidant enzymes such as hepatic SOD, CAT, and GSH-Px, which protect the cell from oxidative damage (Harman, 1991; Dröge, 2002). Quercetin directly degrades the ROS and free radicals which reduce the oxidative stress in women with PCOS (Hanasaki et al., 1994; Boots et al., 2008) (Figure 3.6).

Adipose tissue produce adiponectin, leptin, TNF-α, etc. (Sun et al., 2011). TNF-α and leptin block insulin receptor and IGF-1 receptor tyrosine kinases by inhibiting serine phosphorylation of IRS-1 which causes obese conditions in women with PCOS (Hotamisligil et al., 1996). However, quercetin increases the tyrosine phosphorylation of IRS-1 (Eid and Haddad, 2017) and induces pancreatic β-cell proliferation which leads to increase in the insulin level (Gurav et al., 2018). On the other hand, adiponectin enhances insulin sensitivity (Mamaghani et al., 2009; Cui et al., 2017) but its level is low in women with PCOS because testosterone concentration is higher in women

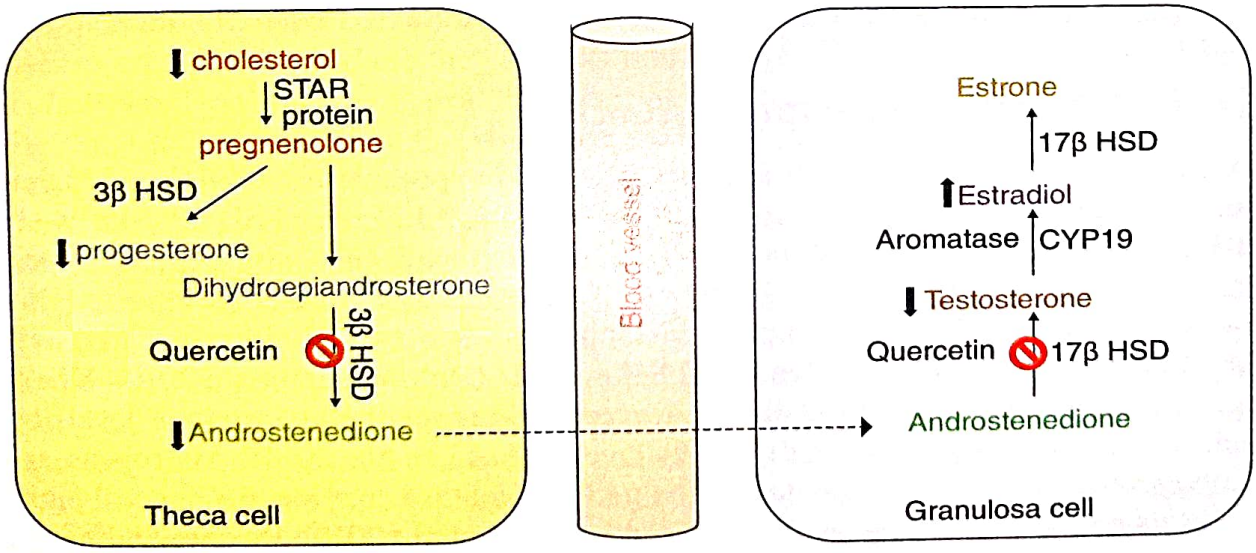
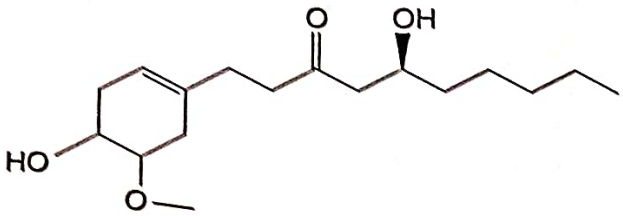


FIGURE 3.6 Effects of quercetin on steroidogenesis during PCOS.

with PCOS which exerts negative feedback on adiponectin secretion (Rezvan et al., 2017). Therefore, it decreases insulin sensitivity and increases insulin resistance condition in women with PCOS. However, quercetin increases adiponectin production by decreasing TNF α synthesis through the inhibition of NF-κβ (Min et al., 2007). Shah and Patel reported that correction of dyslipidemia decreased plasma concentrations of cholesterol, reduced triglyceride, LDL, and VLDL levels, and increased the HDL level due to the administration of quercetin (Shah and Patel, 2016). Hong and his associates reported that quercetin decreases the serum glucose level to maintain glucose homeostasis and reduces body weight by decreasing the production of steroidogenic enzymes such as 3β-HSD and 17-β HSD (Hong et al., 2018). Antiobesity action of quercetin reduces adipogenesis and lipogenesis by decreasing the expression of PPARγ, SREBP, and fatty acid synthase in adipocytes, thereby reducing body fat and protecting against weight gain (Ahn et al., 2008; Aguirre et al., 2011).

3.4.2 6-Gingerol

Ginger rhizome, commonly known as ginger, contains pungent phenolic substances 6-gingerol (Kim et al., 2005). The chemical name of 6-gingerol is – (1-[4′-hydroxy-3′-methoxyphenyl]5-hydroxy-3-decanone). It is the ginger extract in natural aromatic polyphenol. It is the most bioactive compound of ginger, having different biological properties such as anticancer, antioxidant, antiatherosclerosis, anti-inflammation, antiplatelet aggression, and antifungal properties (Pournaderi et al., 2017a).



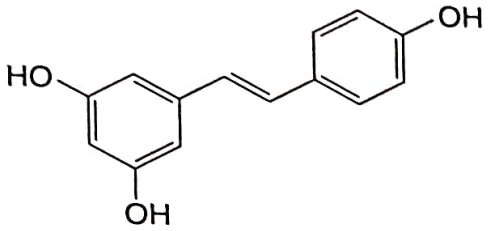
Structure of 6-gingerol

3.4.3 6-Gingerol as Phytotherapeutics

In women with PCOS, high-pituitary sensitivity to hypothalamic GnRH and higher pulse frequency of GnRH increases the production of LH over FSH (Polska et al., 2011). A rise in level produced more androgen from thecal cells which causes hyperandrogenism in PCOS patients (Moret et al., 2009). Rahmanian et al. reported that 6-gingerol suppresses gonadotropin secretion by its effect on pituitary-gonadal axis which in turn decreases the release of FSH and LH (Rahmanian et al., 2012). Khaki and his coresearchers reported that 6-gingerol decreases the testosterone levels by reducing the blood-glucose and insulin level (Khaki et al., 2014). Androgens are synthesized into estrogen by cytochrome p450 aromatase enzyme. 6-Gingerol hampers this pathway and reduces the estrogen level (Li et al., 2013). Prostaglandins are responsible for gonadotropin synthesis. Pournaderi and his coresearchers reported that 6-gingerol inhibits the synthesis of arachidonic acid and prostaglandins by inhibiting cyclooxygenase and lipoxygenase pathways, thereby normalizing the hormonal imbalance and decreasing the gonadotropin level.

3.4.4 Resveratrol

Resveratrol (trans-3,5,4′-tryhydroxystilbene) is a natural polyphenol of stilbene family and is synthesized from phenylalanine (Fernández-Mar et al., 2012). It can be extracted from the skin and seeds of grapes, peanuts and their derivatives, barriers, dark chocolate, and the derivatives of red wine, rose wine, and white wine (Fernández-Mar et al., 2012). Its concentration is higher in red wine (1.90 mg/l) than white wine (0.13 mg/l) and rose wine (0.41 mg/l) (Romero-Pérez et al., 1996; Carando et al., 1999; Landrault et al., 2002; Stervbo et al., 2006). It has two isomeric forms: cis and trans-resveratrol. The trans-resveratrol is found in grapevines which is the main component of stilbene family of phenolic compound. It has anticarcinogenic, antiproliferative, anti-inflammatory, and antioxidant properties (Wong et al., 2010).



Structure of Resveratrol

3.4.4.1 Resveratrol as Phytotherapeutics

Resveratrol is a nonflavonoid polyphenol. This phytoestrogen exhibits antidiabetic, antioxidant, anti-inflammatory (Furat Rencber et al., 2018) and chemopreventive properties (Ortega et al., 2012). Yet not much research has been done regarding the role of resveratrol in reproductive function such as PCOS.

Ortega and associates reported that resveratrol protects the granulosa cell, embryonic cell, and erythroleukemia cells from apoptosis (Ortega et al., 2012). In theca-interstitial cell, LH binds with LH receptor which converts cholesterol to pregnenolone and then ovarian androgen (i.e. androstenedione and some testosterone), which then diffuses to granulosa cell where they convert into estrogen by aromatase enzyme (Hillier et al., 1994). However, in the granulosa cell of PCOS, women have little or no aromatase (P_{450}) activity; therefore E_2 production decreases (Erickson et al., 1990). In women with PCOS, theca cell produces more testosterone than the normal theca cell because of high levels of LH concentration. The resveratrol supplement inhibits mRNA expression of Cyp17a1 (rate-limiting enzyme in androgen biosynthesis pathway) in theca cells, thereby decreasing the excessive production of ovarian androgen or steroidogenesis from thecal cells (Ortega and Duleba, 2015; Mansour et al., 2021). Resveratrol can inhibit theca cell proliferation and increase the growth of granulosa cell (Mansour et al., 2021). As a result, the estrogen level can return to its normal condition. Hence, ultimately decline the total testosterone quantity and DHEAS level and improve ovulation in women with PCOS. Granulosa cells in women with PCOS also produced an increased amount of AMH from preantral and small antral follicles but there was no effect in AMH expression after giving resveratrol supplement (Ortega et al., 2012).

Two factors of insulin resistance, i.e., enlarged adipocytes and decreased lipolytic activity, are associate with PCOS (Faulds et al., 2003; Mannerås-Holm et al., 2011). Resveratrol reduce lipogenesis and increase release of free fatty acid (FFA) and

induce lipolysis by decreasing lipogenic enzyme activity and by stimulating adipose triglyceride lipase (ATGL) (Alberdi et al., 2011; Lasa et al., 2012). These adipose triglyceride lipases hydrolyze triglyceride to form diglyceride and FFA (Lasa et al., 2012), hence decrease fat mass gain and reduce adiposity by resveratrol supplement (Benrick et al., 2013). Resveratrol supplement shows no effect on the circulating level of SHBG and lipid metabolism in PCOS patients (Mansour et al., 2021).

Wong and coresearchers reported that resveratrol counteracts antiapoptotic effects of insulin and oxidative stress (Wong et al., 2010). Insulin and moderate oxidative stress stimulate theca-interstitial cell of ovaries to grow excessively (Duleba et al., 1997; Duleba et al., 2004). Hence, the ovaries are enlarged in women with PCOS women (Hughesdon, 1982). But resveratrol inhibits excess theca-interstitial cell proliferation by inducing apoptosis through increasing caspase 3/7 activity and DNA fragmentation (Joe et al., 2002; Jiang et al., 2005). Resveratrol also inhibits the growth of theca cell by increasing the insulin sensitivity and decreasing insulin resistance and oxidative stress (Baur et al., 2006; Ortega et al., 2012).

Resveratrol supplement can reduce body weight and obesity by reducing inflammatory markers (IL-1β, IL-6, TNF-α), adipocyte proliferation, lipogenesis, and promoting adipocyte apoptosis, lipolysis, and fatty acid oxidation (Christenson et al., 2016). According to Ortega and his coworkers, vascular endothelial growth factor (VEGF) is a key proangiogenic factor involved in the regulation of follicular maturation in granulosa cell which is activated by HIF1 genes and present at high level in women with PCOS (Stelzer et al., 2016). LH stimulates VEGF expression in the granulosa cell of the ovaries (Artini et al., 2003). As the LH level is higher in women with PCOS, higher VEGF expression is found in women with PCOS which gets negative impact on follicular maturation and decreases the ability of fertilization (de Leo et al., 2016). According to Bahramrezaie and his associates, resveratrol supplement can decrease VEGF mRNA and protein expression by decreasing HIF1 expression and by reducing the LH level in women with PCOS (Bahramrezaie et al., 2019; Ortega et al., 2012) (Figure 3.7).

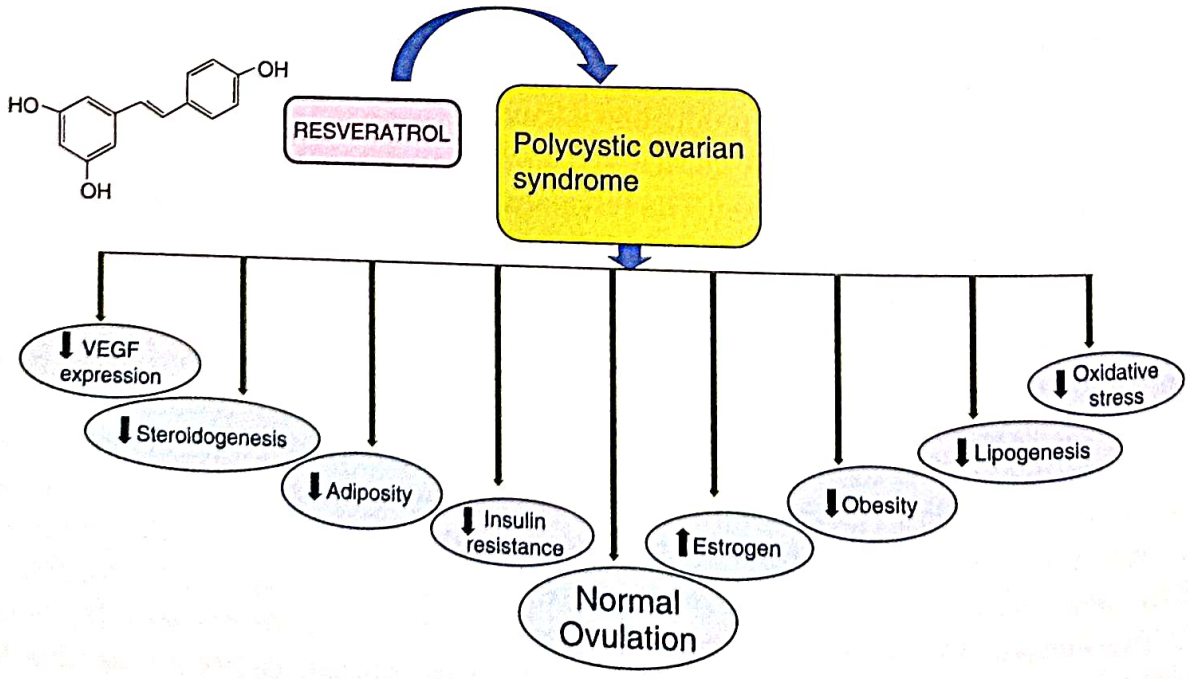


FIGURE 3.7 Schematic diagram showing effect of resveratrol in PCOS management.

3.5 CONCLUSION

PCOS is a complex metabolic and reproductive disorder with many complications, such as anovulation, diabetes, cardiovascular, so on. Numerous synthetic or allopathic drugs are available for the treatment of PCOS but they all have various side effects following long-term administration. Therefore, pure plant-derived bioactive compounds such as resveratrol, quercetin, and 6-gingerol could be the safest alternatives with higher therapeutic potential for PCOS management. This review has led to establish that these bioactive compounds may regulate and reverse PCOS to normal ovulation/reproductive cyclicity/menstrual cycles and other associated metabolic disorders. However, before reaching to any conclusion further, clinical investigations are required to standardize the pharmacological properties of these herbal remedies to be employed for the treatment of PCOS, or as an adjuvant therapy to make it beneficial for humans to examine the therapeutic potential.

BIBLIOGRAPHY

Aguirre, L, Arias, N, Macarulla, M T, Gracia, A, & Portillo, M P (2011). Beneficial effects of quercetin on obesity and diabetes. *The Open Nutraceuticals Journal*, 4(1), 189–198.

Ahn, J, Lee, H, Kim, S, Park, J, & Ha, T (2008). The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signalling pathways. *Biochemical and Biophysical Research Communications*, 373(4), 545–549, https://doi.org/10.1016/j.bbrc.2008.06.077.

Alberdi, G, Rodríguez, V M, Miranda, J, Macarulla, M T, Arias, N, Andrés-Lacueva, C, & Portillo, M P (2011). Changes in white adipose tissue metabolism induced by resveratrol in rats. *Nutrition & Metabolism*, 8(1), 1–7, https://doi.org/10.1186/1743-7075-8-29.

Artini, P G, Monti, M, Cristello, F, Matteucci, C, Bruno, S, Valentino, V, & Genazzani, A R (2003). Vascular endothelial growth factor in females of reproductive age. *Gynecological Endocrinology: The Official Journal of the International Society of Gynecological Endocrinology*, 17(6), 477–492, https://doi.org/10.1080/09513590312331290418.

Bahramrezaie, M, Amidi, F, Aleyasin, A, Saremi, A T, Aghahoseini, M, Brenjian, S, Khodarahmian, M, & Pooladi, A (2019). Effects of resveratrol on VEGF & HIF1 genes expression in granulosa cells in the angiogenesis pathway and laboratory parameters of polycystic ovary syndrome: a triple-blind randomized clinical trial. *Journal of Assisted Reproduction and Genetics*, 36(8), 1701–1712, https://doi.org/10.1007/s10815-019-01461-6.

Basheer, M, Rai, S, Ghosh, H, & Hajam, Y A (2018). Protective role of seed extract of Tephrosia purpurea in letrozole induced polycystic ovary syndrome in Wistar rats. *Journal of Biological Sciences*, 18(8), 458–467.

Baur, J, Pearson, K, & Price, N (2006). Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*, 444, 337–342.

Benrick, A, Maliqueo, M, Miao, S, Villanueva, J A, Feng, Y, Ohlsson, C, Duleba, A J, & Stener-Victorin, E (2013). Resveratrol is not as effective as physical exercise for improving reproductive and metabolic functions in rats with dihydrotestosterone-induced polycystic ovary syndrome. *Evidence-Based Complementary and Alternative Medicine*, https://doi.org/10.1155/2013/964070.

Benson, S, Hahn, S, Tan, S, Mann, K, Janssen, O E, Schedlowski, M, & Elsenbruch, S (2009). Prevalence and implications of anxiety in polycystic ovary syndrome: results of an internet-based survey in Germany. *Human Reproduction*, 24(6), 1446–1451, https://doi.org/10.1093/humrep/dep031.

Boots, A W, Haenen, G R M M, & Bast, A (2008). Health effects of quercetin: from antioxidant to nutraceutical. *European Journal of Pharmacology*, 585(2–3), 325–337, https://doi.org/10.1016/j.ejphar.2008.03.008.

Carando, S, Teissedre, P L, Waffo-Teguo, P, Cabanis, J C, Deffieux, G, & Merillon, J M (1999). High-performance liquid chromatography coupled with fluorescence detection for the determination of trans-astringin in wine. *Journal of Chromatography A*, 849(2), 617–620.

Cedars, M I, Steingold, K A, de Ziegler, D, Lapolt, P S, Chang, R J, & Judd, H L (1992). Long-term administration of gonadotropin-releasing hormone agonist and dexamethasone: assessment of the adrenal role in ovarian dysfunction. *Fertility and Sterility*, 57(3), 495–500, https://doi.org/10.1016/s0015-0282(16)54890-0.

Choi, S H, Shapiro, H, Robinson, G E, Irvine, J, Neuman, J, Rosen, B, Murphy, J, & Stewart, D (2005). Psychological side-effects of clomiphene citrate and human menopausal gonadotrophin. *Journal of Psychosomatic Obstetrics and Gynaecology*, 26(2), 93–100, https://doi.org/10.1080/01443610400022983.

Christenson, J, Whitby, S J, Mellor, D, Thomas, J, McKune, A, Roach, P D, & Naumovski, N (2016). The effects of resveratrol supplementation in overweight and obese humans: a systematic review of randomized trials. *Metabolic Syndrome and Related Disorders*, 14(7), 323–333, https://doi.org/10.1089/met.2016.0035.

Coffey, S, Bano, G, & Mason, H D (2006). Health-related quality of life in women with polycystic ovary syndrome: a comparison with the general population using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) and the Short Form-36 (SF-36). *Gynaecological Endocrinology*, 22(2), 80–86.

Cui, Z, Sheng, T, Wang, Y, Zhou, W, Wang, W, Jin, Y, Jin, Y, Zhang, Z, Jin, X, & Yang, K (2017). Association between single nucleotide polymorphisms (SNPs) in the gene of ADP-ribosylation factor-like 15 (ARL15) and type 2 diabetes (T2D) in Korean Chinese population in Yanbian, China. *International Journal of Diabetes in Developing Countries*, 37(2), 124–128, https://doi.org/10.1007/s13410-015-0391-3.

Das, M, Djahanbakhch, O, Hacihanefioglu, B, Saridogan, E, Ikram, M, Ghali, L, Raveendran, M, & Storey, A (2008). Granulosa cell survival and proliferation are altered in polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism*, 93(3), 881–887, https://doi.org/10.1210/jc.2007-1650.

de Leo, V, Musacchio, M C, Cappelli, V, Massaro, M G, Morgante, G, & Petraglia, F (2016). Genetic, hormonal and metabolic aspects of PCOS: an update. *Reproductive Biology and Endocrinology*, 14(1), https://doi.org/10.1186/s12958-016-0173-x.

Doi, S A R, Al-Zaid, M, Towers, P A, Scott, C J, & Al-Shoumer, K A S (2005). Irregular cycles and steroid hormones in polycystic ovary syndrome. *Human Reproduction*, 20(9), 2402–2408, https://doi.org/10.1093/humrep/dei093.

Dröge, W (2002). Free radicals in the physiological control of cell function. *Physiological Reviews*, 82(1), 47–95, https://doi.org/10.1152/physrev.00018.2001.

Duleba, A, Spaczynski, R Z, Olive, D L, & Behrman, H R (1997). Effects of insulin and insulin-like growth factors on proliferation of rat ovarian theca-interstitial cells. *Biology of Reproduction*, 56(4), 891–897.

Duleba, A J, Foyouzi, N, Karaca, M, Pehlivan, T, Kwintkiewicz, J, & Behrman, H R (2004). Proliferation of ovarian theca-interstitial cells is modulated by antioxidants and oxidative stress. *Human Reproduction*, 19(7), 1519–1524, https://doi.org/10.1093/humrep/deh299.

Eid, H, & Haddad, P (2017). The antidiabetic potential of quercetin: underlying mechanisms. *Current Medicinal Chemistry*, 24(4), 355–364.

Erickson, G F, Magoffin, D A, Cragun, J R, & Chang, R J (1990). The effects of insulin and insulin-like growth factors-I and-II on estradiol production by granulosa cells of polycystic ovaries. *Journal of Clinical Endocrinology and Metabolism*, 70(4), 894–902.

Faulds, G, Rydé N M, Ek, I, Wahrenberg, H, & Arner, P (2003). Mechanisms behind lipolytic catecholamine resistance of subcutaneous fat cells in the polycystic ovarian syndrome. *The Journal of Clinical Endocrinology & Metabolism*, 88(5), 2269–2273, https://doi.org/10.1210/jc.2002-021573.

Fernández-Mar, M I, Mateos, R, García-Parrilla, M C, Puertas, B, & Cantos-Villar, E (2012). Bioactive compounds in wine: resveratrol, hydroxytyrosol and melatonin: a review. *Food Chemistry*, 130(4), 797–813.

Formica, J V, & Regelson, W (1995). Review of the biology of quercetin and related bioflavonoids. *Food and Chemical Toxicology*, 33(12), 1061–1080.

Furat Rencber, S, Kurnaz Ozbek, S K, Eraldemir, C, Sezer, Z, Kum, T, Ceylan, S, & Guzel, E (2018). Effect of resveratrol and metformin on ovarian reserve and ultrastructure in PCOS: an experimental study. *Journal of Ovarian Research*, 11(1), 1–16. https://doi.org/10.1186/s13048-018-0427-7.

Gambineri, A, Pelusi, C, Vicennati, V, Pagotto, U, & Pasquali, R (2002). Review obesity and the polycystic ovary syndrome. *International Journal of Obesity*, 26, 883–896. https://doi.org/10.1038=sj.ijo=0801994.

Gurav, M, Bhise, S, & Warghade, S (2018). Effect of quercetin on beta cell regeneration. *Asian Journal of Pharmacy and Pharmacology*, 4(2), 214–221. https://doi.org/10.31024/ajpp.2018.4.2.19.

Knochenhauer, E S, Key, T J, Kahsar-Miller, M, Waggoner, W, Boots, L R, & Azziz, R (1998). Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *The Journal of Clinical Endocrinology and Metabolism*, 83(9), 3078–3082. https://academic.oup.com/jcem/article/83/9/3078/2865186.

Hanasaki, Y, Ogawa, S, & Fuku, S (1994). The correlation between active oxygens scavenging and antioxidative effects of flavonoids. *Free Radical Biology & Medicine*, 16(6) 845–850.

Harman, D (1991). The aging process: major risk factor for disease and death. *Proceedings of the National Academy of Sciences*, 88(12), 5360–5363.

Hillier, S G, Whitelaw, P F, & Smyth, C D (1994). Follicular oestrogen synthesis: the "two-cell, two-gonadotrophin" model revisited. *Molecular and Cellular Endocrinology*, 100(1–2), 51–54.

Hong, Y, Yin, Y, Tan, Y, Hong, K, Jiang, F, & Wang, Y (2018). Effect of quercetin on biochemical parameters in letrozole-induced polycystic ovary syndrome in rats. *Tropical Journal of Pharmaceutical Research*, 17(9), 1783–1788. https://doi.org/10.4314/tjpr.v17i9.15.

Hotamisligil, G S, Peraldi, P, Budavari, A, Ellis, R, White, M F, Spiegelman, B M (1996). IRS-1 mediated inhibition of insulin receptor tyrosine kinase activity in TNF-α and obesity-induced insulin resistance. *Science*, 271(5249), 665–670.

Hughesdon, P E (1982). Morphology and morphogenesis of the Stein-Leventhal ovary and of so-called "hyperthecosis". *Obstetrical & Gynecological Survey*, 37(2), 59–77.

Iside, C, Scafuro, M, Nebbioso, A, & Altucci, L (2020). SIRT1 activation by natural phytochemicals: an overview. *Frontiers in Pharmacology*, 11, 1225. https://doi.org/10.3389/fphar.2020.01225.

Jahan, S, Abid, A, Khalid, S, Afsar, T, Ain, Q U, Shaheen, G, Almajwal, A, & Razak, S (2018). Therapeutic potentials of quercetin in management of polycystic ovarian syndrome using letrozole induced rat model: a histological and a biochemical study. *Journal of Ovarian Research*, 11(1), 1–10. https://doi.org/10.1186/s13048-018-0400-5.

Jeong, S M, Kang, M J, Choi, H N, Kim, J H, & Kim, J I (2012). Quercetin ameliorates hyperglycemia and dyslipidemia and improves antioxidant status in type 2 diabetic db/db mice. *Nutrition Research and Practice*, 6(3), 201–207. https://doi.org/10.4162/nrp.2012.6.3.201.

Jiang, H, Zhang, L, Kuo, J, Kuo, K, Gautam, S C, Groc, L, Rodriguez, A I, Koubi, D, Hunter, T J, Corcoran, G B, Seidman, M D, & Levine, R A (2005). Resveratrol-induced apoptotic death in human U251 glioma cells. *Molecular Cancer Therapeutics*, 4(4), 554–561. http://aacrjournals.org/mct/article-pdf/4/4/554/1870417/554-561.pdf.

Joe, A K, Liu, H, Suzui, M, Vural, M E, Xiao, D, Weinstein, I B, & Of Medicine, D (2002). Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. *Clinical Cancer Research*, 8(3), 893–903. http://aacrjournals.org/clincancerres/article-pdf/8/3/893/2302892/df0302000893.pdf.

Joshi, B, Mukherjee, S, Patil, A, Purandare, A, Chauhan, S, & Vaidya, R (2014). A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. *Indian Journal of Endocrinology and Metabolism*, 18(3), 317–324, https://doi.org/10.4103/2230-8210.131162.

Kafali, H, Iriadam, M, Ozardali, I, & Demir, N (2004). Letrozole-induced polycystic ovaries in the rat: a new model for cystic ovarian disease. *Archives of Medical Research*, 35(2), 103–108, https://doi.org/10.1016/j.arcmed.2003.10.005.

Khaki, A, Khaki, A A, Hajhosseini, L, Golzar, F S, & Ainehchi, N (2014). The anti-oxidant effects of ginger and cinnamon on spermatogenesis dys-function of diabetes rats. *African Journal of Traditional, Complementary and Alternative Medicines*, 11(4), https://doi.org/10.4314/ajtcam.v11i4.1.

Kim, E C, Min, J K, Kim, T Y, Lee, S J, Yang, H O, Han, S, Kim, Y M, & Kwon, Y G (2005). [6]-Gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. *Biochemical and Biophysical Research Communications*, 335(2), 300–308, https://doi.org/10.1016/j.bbrc.2005.07.076.

Kim, J H, Kang, M J, Choi, H N, Jeong, S M, Lee, Y M, & Kim, J I (2011). Quercetin attenuates fasting and postprandial hyperglycemia in animal models of diabetes mellitus. *Nutrition Research and Practice*, 5(2), 107–111, https://doi.org/10.4162/nrp.2011.5.2.107.

Krishnan, A, & Muthusami, S (2017). Hormonal alterations in PCOS and its influence on bone metabolism. *Journal of Endocrinology*, 232 (2), R99–R113, https://doi.org/10.1530/JOE-16-0405.

Landrault, N, Larronde, F, Delaunay, J C, Castagnino, C, Vercauteren, J, Merillon, J M, Gasc, F, Cros, G, & Teissedre, P L (2002). Levels of stilbene oligomers and astilbin in French varietal wines and in grapes during noble rot development. *Journal of Agricultural and Food Chemistry*, 50(7), 2046–2052.

Lasa, A, Schweiger, M, Kotzbeck, P, Churruca, I, Simón, E, Zechner, R, & Portillo, M d P (2012). Resveratrol regulates lipolysis via adipose triglyceride lipase. *Journal of Nutritional Biochemistry*, 23(4), 379–384.

Leventhal, M L (1958). The Stein-Leventhal syndrome. *American Journal of Obstetrics and Gynecology*, 76(4), 825–838, https://doi.org/10.1016/0002-9378(58)90019-X.

Leventhal, M L, & Cohen, M R (1951). Bilateral polycystic ovaries the Stein syndrome. *American Journal of Obstetrics and Gynecology*, 61(5), 1034–1046, https://doi.org/10.1016/0002-9378(51)90305-5.

Li, M, Chen, P-Z, Yue, Q-X, Li, J-Q, Chu, R-A, Zhang, W, & Wang, H (2013). Pungent ginger components modulate human cytochrome P450 enzymes in vitro. *Acta Pharmacologica Sinica*, 34(9), 1237–1242, https://doi.org/10.1038/aps.2013.49.

Lin, D, Xiao, M, Zhao, J, Li, Z, Xing, B, Li, X, Kong, M, Li, L, Zhang, Q, Liu, Y, Chen, H, Qin, W, Wu, H, & Chen, S (2016). An overview of plant phenolic compounds and their importance in human nutrition and management of type 2 diabetes. *Molecules*, 21(10), 1374, https://doi.org/10.3390/molecules21101374.

Linares, R, Hernández, D, Morán, C, Chavira, R, Cárdenas, M, Domínguez, R, & Morales-Ledesma, L (2013). Unilateral or bilateral vagotomy induces ovulation in both ovaries of rats with polycystic ovarian syndrome. *Reproductive Biology and Endocrinology*, 11(1), 1–9, https://doi.org/10.1186/1477-7827-11-68.

Macgregor, A H, Johnson, J E, & Bunde, C A (1968). Further clinical experience with clomiphene citrate. *Fertility and Sterility*, 19(4), 616–622.

Macut, D, Pfeifer, M, Yildiz, B O, & Diamanti-Kandarakis, E (eds) (2013). *Polycystic Ovary Syndrome: Novel Insights into Causes and Therapy*. Front Horm Res series. Basel: Karger, 2013, vol. 40, pp. 51–63. https://doi.org/10.1159/000342244Mamaghani, F, Zarghami, N, Maleki, M J, Moghaddam M, & Pourhassan F (2009). Variation of adiponectin levels in normal and obese subjects: possible correlation with lipid profiles. *International Journal of Endocrinology and Metabolism*, 7(3), 170–178.

Manneråas-Holm, L, Leonhardt, H, Kullberg, J, Jennische, E, Odé, A, Ran Holm, G, Hellströ, M, Lö, L, Olivecrona, G, Stener-Victorin, E, & Lö, M (2011). Adipose tissue has aberrant morphology and function in PCOS: enlarged adipocytes and low serum adiponectin, but not circulating sex steroids, are strongly associated with insulin resistance. *The Journal of Clinical Endocrinology & Metabolism*, 96(2), E304–E311, https://doi.org/10.1210/jc.2010-1290.

Mansour, A, Samadi, M, Sanginabadi, M, Gerami, H, Karimi, S, Hosseini, S, Shirzad, N, Hekmatdoost, A, Mahdavi-Gorabi, A, Mohajeri-Tehrani, M R, & Qorbani, M (2021). Effect of resveratrol on menstrual cyclicity, hyperandrogenism and metabolic profile in women with PCOS. *Clinical Nutrition*, 40(6), 4106–4112, https://doi.org/10.1016/j.clnu.2021.02.004.

Maritim, A C, Sanders, R A, & Watkins, J B (2003). Diabetes, oxidative stress, and antioxidants: a review. *Journal of Biochemical and Molecular Toxicology*, 17(1), 24–38, https://doi.org/10.1002/jbt.10058.

Mihanfar, A, Nouri, M, Roshangar, L, & Khadem-Ansari, M H (2021a). Polyphenols: natural compounds with promising potential in treating polycystic ovary syndrome. *Reproductive Biology*, 21(2), 100500, https://doi.org/10.1016/j.repbio.2021.

Mihanfar, A, Nouri, M, Roshangar, L, & Khadem-Ansari, M H (2021b). Therapeutic potential of quercetin in an animal model of PCOS: possible involvement of AMPK/SIRT-1 axis. *European Journal of Pharmacology*, 900, https://doi.org/10.1016/j.ejphar.2021.174062.

Min, Y D, Choi, C H, Bark, H, Son, H Y, Park, H H, Lee, S, Park, J W, Park, E K, Shin, H I, & Kim, S H (2007). Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-κB and p38 MAPK in HMC-1 human mast cell line. *Inflammation Research*, 56(5), 210–215, https://doi.org/10.1007/s00011-007-6172-9.

Moret, M, Stettler, R, Rodieux, F, Gaillard, R C, Waeber, G, Wirthner, D, Giusti, V, Tappy, L, & Pralong, F P (2009). Insulin modulation of luteinizing hormone secretion in normal female volunteers and lean polycystic ovary syndrome patients. *Neuroendocrinology*, 89(2), 131–139, https://doi.org/10.1159/000160911.

Morley, L C, Tang, T, Yasmin, E, Norman, R J, & Balen, A H (2017). Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database of Systematic Reviews*, (11), 1465–1858. https://doi.org/10.1002/14651858.CD003053.pub6

Nejabati, H R, Samadi, N, Shahnazi, V, Mihanfar, A, Fattahi, A, Latifi, Z, Bahrami-asl, Z, Roshangar, L, & Nouri, M (2020). Nicotinamide and its metabolite N1-methylnicotinamide alleviate endocrine and metabolic abnormalities in adipose and ovarian tissues in rat model of polycystic ovary syndrome. *Chemico-Biological Interactions*, 324, 109093, https://doi.org/10.1016/j.cbi.2020.109093.

Ortega, I, & Duleba, A J (2015). Ovarian actions of resveratrol. *Annals of the New York Academy of Sciences*, 1348(1), 86–96, https://doi.org/10.1111/nyas.12875.

Ortega, I, Wong, D H, Villanueva, J A, Cress, A B, Sokalska, A, Stanley, S D, & Duleba, A J (2012). Effects of resveratrol on growth and function of rat ovarian granulosa cells. *Fertility and Sterility*, 98(6), 1563–1573.

Pellatt, L, Hanna, L, Brincat, M, Galea, R, Brain, H, Whitehead, S, & Mason, H (2007). Granulosa cell production of anti-Müllerian hormone is increased in polycystic ovaries. *The Journal of Clinical Endocrinology and Metabolism*, 67(3), 460–464, https://doi.org/10.1210/jc.2006-1582.

Pigny, P, Merlen, E, Robert, Y, Cortet-Rudelli, C, Decanter, C, Jonard, S, & Dewailly, D (2003). Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. *The Journal of Clinical Endocrinology & Metabolism*, 88(12), 5957–5962, https://doi.org/10.1210/jc.2003-030727.

Piparva, K G, & Buch, J G (2011). Deep vein thrombosis in a woman taking oral combined contraceptive pills. *Journal of Pharmacology & Pharmacotherapeutics*, 2(3), 185.

Plymate, S R, Matej, L A, Jones, R E, & Friedl, K E (1988). Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. *The Journal of Clinical Endocrinology and Metabolism*, 67(3), 460–464.

Polska, E, Lewiński, A, Lewandowski, K C, Cajdler-Łuba, A, Salata, I, & Bieńkiewicz, M (2011). The utility of the gonadotrophin releasing hormone (GnRH) test in the diagnosis of polycystic ovary syndrome (PCOS). *Endokrynologia Polska*, 62(2), 120–128.

Poretsky, L, Cataldo, N A, Rosenwaks, Z, & Giudice, L C (1999). The insulin-related ovarian regulatory system in health and disease. *Endocrine Reviews*, 20(4), 535–582, https://doi.org/10.1210/edrv.20.4.0374.

Poretsky, L, Chandrasekher, Y A, Bai, C, Liu, H C, Rosenwaks, Z, & Giudice, L (1996). Insulin receptor mediates inhibitory effect of insulin, but not of insulin-like growth factor (IGF)-I, on IGF binding protein 1 (IGFBP-1) production in human granulosa cells. *The Journal of Clinical Endocrinology & Metabolism*, 81(2), 493–496, https://academic.oup.com/jcem/article/81/2/493/2649361.

Pournaderi, P S, Yaghmaei, P, Khodaei, H, Noormohammadi, Z, & Hejazi, S H (2017a). The effects of 6-gingerol on reproductive improvement, liver functioning and cyclooxygenase-2 gene expression in estradiol valerate – induced polycystic ovary syndrome in Wistar rats. *Biochemical and Biophysical Research Communications*, 484(2), 461–466, https://doi.org/10.1016/j.bbrc.2017.01.057.

Pourteymour Fard Tabrizi, F, Hajizadeh-Sharafabad, F, Vaezi, M, Jafari-Vayghan, H, Alizadeh, M, & Maleki, V (2020). Quercetin and polycystic ovary syndrome, current evidence and future directions: a systematic review. *Journal of Ovarian Research*, 13(1), 1–10, https://doi.org/10.1186/s13048-020-0616-z.

Qu, X, & Donnelly, R (2020). Sex hormone-binding globulin (Shbg) as an early biomarker and therapeutic target in polycystic ovary syndrome. *International Journal of Molecular Sciences*, 21, 1–17, https://doi.org/10.3390/ijms21218191.

Rahmanian, F, Jahromi, V H K, & Kargar, H (2012). The effects of ginger hydroalcoholicextract on spermatogenesis process and hormone-pituitary-gonadal axis in immature mice. *Journal of Natural Science, Biology and Medicine*, 10(3), 915–922.

Rai, S, Basheer, M, Ghosh, H, Acharya, D, & Hajam, Y A (2015) Melatonin attenuates free radical load and reverses histologic architect and hormone profile alteration in female rat: an in vivo study of pathogenesis of letrozole induced poly cystic ovary. *Clinical & Cellular Immunology*, 6, 1–8.

Rani, R, Hajam, Y A, Kumar, R, Bhat, R A, Rai, S, & Rather, M A (2022) A landscape analysis of the potential role of polyphenols for the treatment of polycystic ovarian syndrome (PCOS). *Phytomedicine Plus*, 2(1), 100161.

Rezvan, N, Moini, A, Janani, L, Mohammad, K, Saedisomeolia, A, Nourbakhsh, M, Gorgani-Firuzjaee, S, Mazaherioun, M, & Hosseinzadeh-Attar, M J (2017). Effects of quercetin on adiponectin-mediated insulin sensitivity in polycystic ovary syndrome: a randomized placebo-controlled double-blind clinical trial. *Hormone and Metabolic Research*, 49(2), 115–121, https://doi.org/10.1055/s-0042-118705.

Romero-Pérez, A I, Lamuela-Raventós, R M, Waterhouse, A L, & de La Torre-Boronat, M C (1996). Levels of cis-and trans-resveratrol and their glucosides in white and rosé Vitis vinifera wines from Spain. *Journal of Agriculture and Food Chemistry*, 44(8), 2124–2128.

Rosenfield, R L, & Ehrmann, D A (2016). The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. *Endocrine Reviews*, 35(5), 467–520.

Ruderman, N B, Xu, X J, Nelson, L, Cacicedo, J M, Saha, A K, Lan, F, & Ido, Y. (2010). AMPK and SIRT1: a long-standing partnership? *American Journal of Physiology - Endocrinology Metabolism*, 298, 751–760.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised (2003). Consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human Reproduction*. 2004 Jan; 19(1), 41–47.

Sereepapong, W, Suwajanakorn, S, Triratanachat, S, Sampatanukul, P, Pruksananonda, K, Boonkasemsanti, W, & Reinprayoon, D (2000). Effects of clomiphene citrate on the endometrium of regularly cycling women. *Fertility and Sterility*, 73(2), 287–291.

Shah, K N, & Patel, S S (2016). Pharmaceutical biology phosphatidylinositide 3-kinase inhibition: a new potential target for the treatment of polycystic ovarian syndrome. *Pharmaceutical Biology*, 54(6), 975–983, https://doi.org/10.3109/13880209.2015.1091482.

Sharma, P, Hajam, Y A, Kumar, R, & Rai, S (2022) Complementary and alternative medicine for the treatment of diabetes and associated complications: a review on therapeutic role of polyphenols. *Phytomedicine Plus*, 2(1), 100188.

Shikawa, A I, Amashita, H Y, Iemori, M H, Nagaki, E I, Imoto, M K, Kamoto, M O, Suji, H T, Nawaz, A, Emon, M, Ohammadi, A M, & Atori, Y N (2007). Characterization of inhibitors of postprandial hyperglycemia from the leaves of Nerium indicum. *Journal of Nutritional Science and Vitaminology*, 53(2), 166–173.

Sovino, H, Sir-Petermann, T, & Devoto, L (2002). Clomiphene citrate and ovulation induction. *Reproduction Biomedicine Online*, 4(3), 303–310.

Stelzer, G, Rosen, N, Plaschkes, I, Zimmerman, S, Twik, M, Fishilevich, S, Iny Stein, T, Nudel, R, Lieder, I, Mazor, Y, Kaplan, S, Dahary, D, Warshawsky, D, Guan-Golan, Y, Kohn, A, Rappaport, N, Safran, M, & Lancet, D (2016). The GeneCards suite: from gene data mining to disease genome sequence analyses. *Current Protocols in Bioinformatics*, 54(1), 1–30, 1.30.1–1.30.33, https://doi.org/10.1002/cpbi.5.

Stervbo, U, Vang, O, & Bonnesen, C (2006). Time-and concentration-dependent effects of resveratrol in HL-60 and HepG2 cells. *Cell Proliferation*, 39(6), 469–493.

Sun, K, Kusminski, C M, & Scherer, P E (2011). Adipose tissue remodeling and obesity. *The Journal of Clinical Investigation*, 121(6), 2094–2101, https://doi.org/10.1172/JCI45887.

Tao, X, Cai, L, Chen, L, Ge, S, & Deng, X (2019). Effects of metformin and exenatide on insulin resistance and AMPKα-SIRT1 molecular pathway in PCOS rats. *Journal of Ovarian Research*, 12(1), 86, https://doi.org/10.1186/s13048-019-0555-8.

Tasali, E, van Cauter, E, Hoffman, L, & Ehrmann, D A (2008). Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism*, 93(10), 3878–3884, https://doi.org/10.1210/jc.2008-0925.

Teede, H, Deeks, A, & Moran, L (2010). Open access review polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Medicine*, 8(1), 1–10, http://www.biomedcentral.com/1741-7015/8/41.

Veltman-Verhulst, S M, Boivin, J, Eijkemans, M J C, & Fauser, B J C M (2012). Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies. *Human Reproduction Update*, 18(6), 638–651, https://doi.org/10.1093/humupd/dms029.

Wang, F, Yu, B, Yang, W, Liu, J, Lu, J, & Xia, X (2012). Polycystic ovary syndrome resembling histopathological alterations in ovaries from prenatal androgenized female rats. *Journal of Ovarian Research*, 5(1), 1–7, https://doi.org/10.1186/1757-2215-5-15.

Wong, D H, Villanueva, J A, Cress, A B, & Duleba, A J (2010). Effects of resveratrol on proliferation and apoptosis in rat ovarian theca-interstitial cells. *Molecular Human Reproduction*, 16(4), 251–259, https://doi.org/10.1093/molehr/gaq002.