Herbal Medicine Applications for Polycystic Ovarian Syndrome

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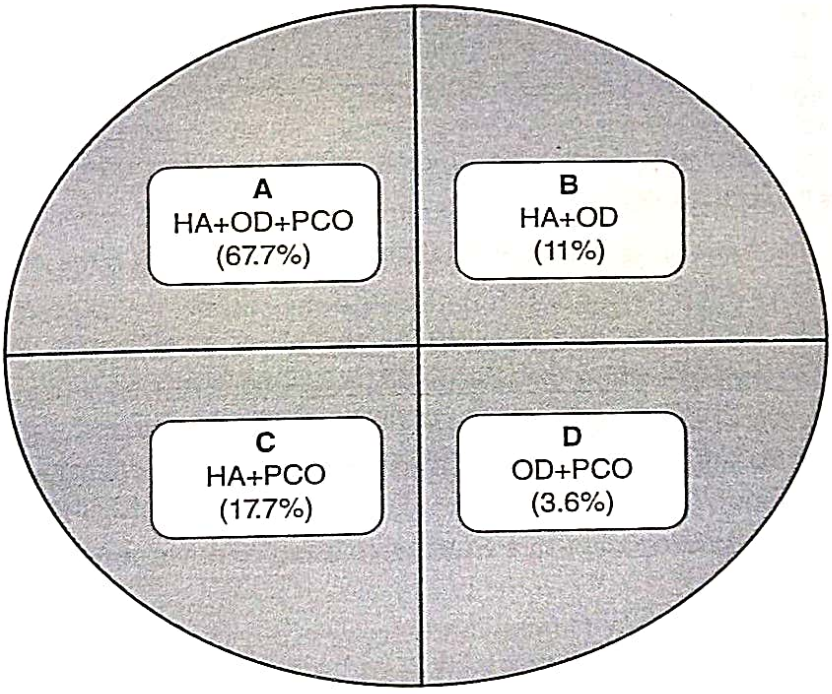
6.1 INTRODUCTION

Polycystic ovarian syndrome (PCOS), also known as Stein–Leventhal syndrome, was first reported in 1935 by Stein and Leventhal. However, Vallisneri, in 1721, an Italian scientist, described a married, infertile woman having shiny ovaries with a white surface, and the size of ovaries was similar to pigeon eggs (Leventhal, 1958; Insler and Lunenfeld, 1990; Knochenhauer et al., 1998). Polycystic ovary syndrome is a fast-spreading endocrine and metabolic abnormality among women of reproductive age, characterized by hyperandrogenism, insulin resistance, obesity, infertility, chronic anovulation, menstrual irregularities, and hirsutism (Allahbadia and Merchant, 2011; Rai et al., 2015; Rani et al., 2022). Women with PCOS have many small cysts of size exceeding 0.5 cm in ovaries and its symptoms varies from women to women (Akkasheh et al., 2016). PCOS is negatively affected by certain factors which are diet, lifestyle, and exposure to environmental toxins. The features of PCOS are evident from prepubertal age until the postmenopausal years, and they can change over the lifespan or overlap each other (Papadakis et al., 2021). According to US National Institutes of Health (NIH) diagnostic criteria (1990), the average rate of PCOS in women of reproductive age from United States, Europe, Asia, and Australia ranges between 5% and 9% (Azziz et al.,

2016). The prevalence rate of PCOS has been reported to be high among Indian women. The pooled prevalence of this disease was found to be about 10% using Rotterdam's criteria and AES (Androgen Excess Society) criteria. However, it was found to be 5.8% using NIH (National Institutes of Health) criteria (Bharali et al., 2022).

There have been several attempts to categorize polycystic ovarian syndrome. According to the National Institutes of Health (NIH) criteria, women having hyperandrogenism and oligo-anovulation were classified to have polycystic ovarian syndrome excluding other endocrine dysfunctions. Later, Rotterdam's expert committee considered the presence of two out of three parameters: oligo-anovulation, clinical hyperandrogenism, and polycystic ovaries in ultrasound. Thus, according to Rotterdam criteria, presence of two out of three following conditions (Szydlarska et al., 2017) are necessary to make PCOS diagnosis:

1. Lack of ovulation or rare ovulation
2. Excessive activity of androgens diagnosed by clinical examination
3. Appearance of polycystic ovaries in the ultrasound after the exclusion of other pathologies characterized by hyperandrogenism.



PHENOTYPE A	HYPERANDROGENISM, OVULATORY DYSFUNCTION AND POLYCYSTIC OVARIES
PHENOTYPE B	HYPERANDROGENISM AND OVULATORY DYSFUNCTION
PHENOTYPE C	HYPERANDROGENISM AND OVULATORY OVARIES
PHENOTYPE D	OVULATORY DYSFUNCTION AND POLYCYSTIC OVARIES

FIGURE 6.1 Phenotypic classification of PCOS recommended by NIH consensus panel (2012).

In 2006, AE-PCOS (Androgen Excess and PCOS Society) defined the diagnosis of PCOS to be based on clinical hyperandrogenism along with oligo-anovulation or polycystic ovaries. Thus, hyperandrogenism remained the main determinant for the diagnosis of PCOS. Finally, NIH consensus panel proposed the following phenotypic approach (Figure 6.1) to categorize PCOS (Sachdeva et al., 2019).

6.2 CAUSES OF POLYCYSTIC OVARIAN SYNDROME (PCOS)

6.2.1 Obesity

Body fat is excessive in PCOS condition. This is because insulin in excess stimulates adipogenesis and abdominal lipogenesis and inhibits lipolysis, leading to adipocyte hypertrophy (Rosenfield, 2020). Obesity is not really a cause of PCOS but it can definitely modify the phenotype of PCOS, specifically visceral adiposity worsens all metabolic and reproductive functions in obese and nonobese women with PCOS (Glueck and Goldenberg, 2019). It has been observed that the body mass index (BMI) and weight gain is higher in women with PCOS as compared with the women who don't have PCOS (Joham et al., 2016; Sharma et al., 2022). Abnormal function of hypothalamic-pituitary-ovarian (HPO) axis which can develop PCOS condition has also been linked to obesity (Legro, 2012). Due to excess adiposity, obese women with PCOS possess additional trouble of insulin resistance, resulting in hyperinsulinemia (Matalliotakis et al., 2006; Louwers and Laven, 2020).

6.2.2 Insulin Resistance

Insulin resistance refers to the reduced response of glucose to a given amount of insulin. It can occur through peripheral target tissue resistance, decreased hepatic clearance, and/or increased pancreatic sensitivity (Balen, 2004). A variety of reproductive abnormalities in women with PCOS are associated with insulin resistance. In normal individuals, the circulating level of insulin is 6–15 μIU/m but in women with PCOS it goes up to 22 μIU/ml, which leads to hyperinsulinemia. This is also responsible for increased level of androgens, ultimately causing insulin resistance and diabetes mellitus along with the development of PCOS (Krishnan and Muthusami, 2017). Insulin directly causes specialized cells in the ovary called thecal cells to produce androgen by the activation of P450c17α (Jeanes and Reeves, 2017). Hyperinsulinemia further exacerbates the pathogenesis of PCOS by inhibiting the production of insulin-like growth factor-1 (IGF-1) binding protein in the liver, leading to elevated circulating levels of IGF-1, which in turn stimulates ovarian thecal cell androgen production (Rosenfield and Ehrmann, 2016).

6.2.3 Hyperandrogenism

The main cause of the elevated ovarian androgen production in PCOS is the follicular theca cells' accelerated androgen synthesis which is caused by the increased expression of many genes encoding steroidogenic enzymes (Basheer et al., 2018). According to estimates, more than 80% of women exhibit hyperandrogenism's signs

and symptoms which include hirsutism, acne, alopecia, and PCOS (Sirmans and Pate, 2013). Research has shown that the main cause of hyperandrogenism in PCOS women is androgen production (Baptiste et al., 2010) from both the ovary (60%) and adrenal (40%). Hyperandrogenism in PCOS may be brought about by impaired intrinsic steroidogenesis in ovarian theca cells or increased LH levels as a result of abnormal hypothalamic-pituitary axis control impacted by insulin (Armanini et al., 2022).

6.2.4 Hormonal Alteration

Neuroendocrine abnormalities appear to play an important role in PCOS pathophysiology with an increase in frequency of GnRH pulses. PCOS patients are known to present a GnRH-generating pulse resistance to negative feedback by progesterone resulting in a higher LH pulses frequency and amplitude (Crespo et al., 2018). Increase GnRH pulse frequency and amplitude can promote LH synthesis over FSH synthesis, leading to a high LH/FSH ratio in women with PCOS. Elevating LH levels plays a vital role in the development of reproductive and metabolic disorders. First, LH promotes the synthesis of androgen in ovarian theca cells, which leads to hyperandrogenism and arrested follicle development. Second, increased LH pulse frequency impairs estrogen and FSH synthesis, thus inhibiting follicle growth and ovulation. Third, LH promotes ovarian secretion of IGF-1, which can further promote LH binding and androgen synthesis in theca cell, and finally it contributes to the formation of polycystic ovaries in PCOS patients (Glueck and Goldenberg, 2019; Liao et al., 2021). Clinically, an altered or abnormal LH/FSH ratio can be utilized as a diagnostic tool to identify early-stage PCOS (Malini and Roy George, 2018). Gonadotropin-releasing hormone (GnRH) pulsatility is disturbed as a result of excessive LH production due to hypothalamic-pituitary-ovarian or adrenal axis dysfunction which also affects the LH/FSH ratio (Figure 6.2). Hypothyroidism (lack of thyroid hormone production by the thyroid gland) is linked to delayed puberty onset, anovulation, amenorrhea, irregular menstrual cycles, infertility, the hyperandrogenism sign, weight gain, and a slight increase in total testosterone levels (de Medeiros et al., 2018; Nath et al., 2019).

6.2.5 Genetic Factors

The genetic basis of polycystic ovarian syndrome (PCOS) was first reported in 1968 by Cooper and colleagues (Khan et al., 2019). Studies of Kahsar-Miller and Cols have suggested an important genetic basis contributing symptoms of PCOS. According to them, first-degree relatives of 93 PCOS patients had a higher risk of being affected in which 35% are nonmenopausal mothers and 40% are sisters. Examining a large twin cohort of monozygotic and dizygotic twin sisters, it has been concluded that genetic components contribute over 70% of PCOS pathogenesis. Hence, it is a complex genetic disease with high inheritance rates (Crespo et al., 2018). A number of genes seem to be involved in PCOS symptoms. Some studies hypothesized that the alteration of expression of specific genes associated with adrenal and ovarian steroidogenesis contribute to hyperandrogenism, e.g., CYP11A1 (coding for P450 cholesterol side-chain cleavage, P450scc), CYP17A1 (coding for 17 alpha hydroxylase and 17,20-lyase), and

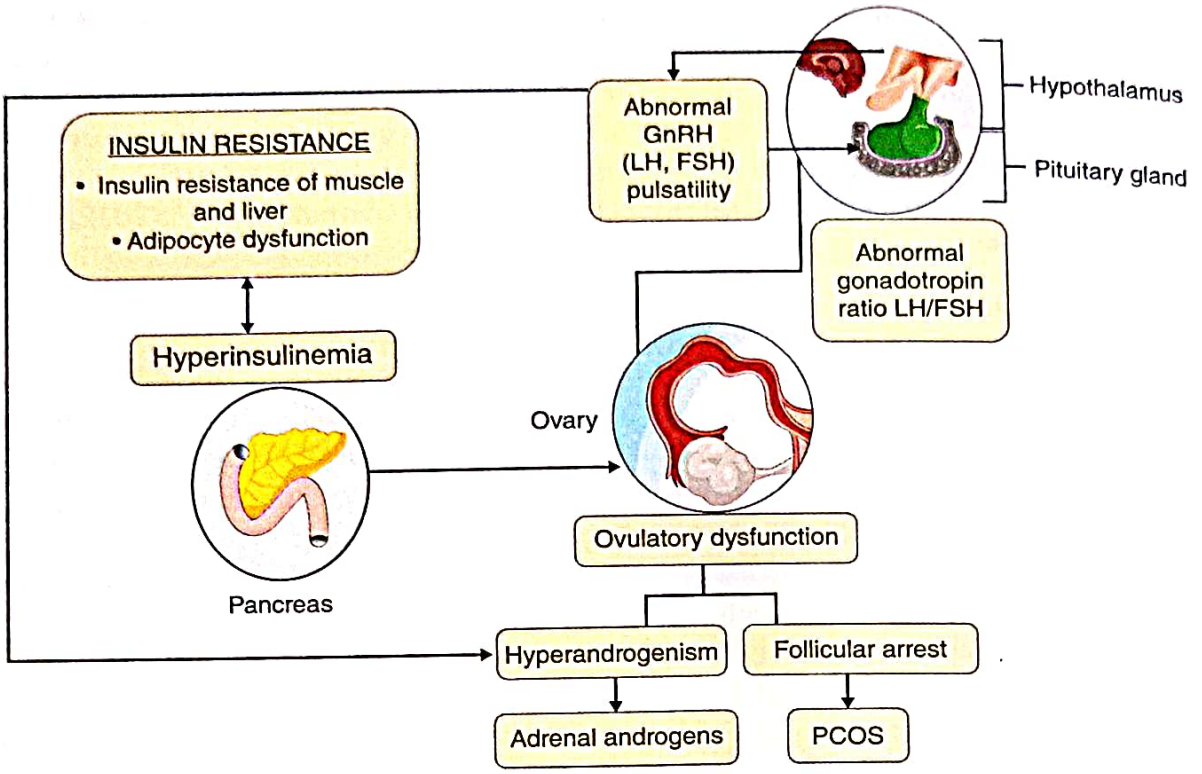


FIGURE 6.2 Pathophysiology of polycystic ovary syndrome (PCOS).

CYP21 (coding for 21-hydroxylase). Some studies suggest DENND1A gene is found in cells of ovarian theca and adrenal glands and its variant is upregulated in theca cells of women with PCOS, favoring androgen excess (Bruni et al., 2022).

6.3 PRESCRIBED TREATMENT FOR PCOS

PCOS condition exhibits disruption in reproductive cycle (primates-menstrual cycle and nonprimates-estrus cycle). Primary treatment in PCOS is lifestyle management, including exercise and balanced diet (Cooney and Dokras, 2017). The type of procedure used in PCOS treatment mainly depends on clinical effects such as infertility treatment, regulation of menstrual disturbances, alleviation of symptoms of hyperandrogenism, or obesity treatment. Women with infertility issues are prescribed to take clomiphene, an estrogen receptor modulator that directly affects the hypothalamic-pituitary axis (Bednarska and Siejka, 2017). A recent metanalysis suggested that letrozole is recommended as the first line treatment for PCOS and infertility (Hoeger et al., 2021). Metformin, an insulin sensitizer, lowers theca cell androgen synthesis *invitro* and has a positive effect on metabolic disturbances and bleeding disorders in women with PCOS. Myoinositol promotes glucose uptake and FSH activity while D-chiro-inositol has a role in androgen synthesis in ovary. Both positively affect the ovarian function in PCOS (Tanbo et al., 2018). Oral contraceptives are the most common options for the treatment of PCOS nowadays (Moini Jazani et al., 2019).

Apart from this, herbal medicines and plant extracts are effective to the condition of PCOS. Presently, conventional therapies are not effective and may have some side effects. Therefore, plant-based drugs especially phytoestrogens are considered

to be comparatively more effective to the condition of PCOS. Traditional practitioners have developed plant-based remedies which are effective on patients with PCOS or amenorrhea and also on underlying metabolic dysfunctions (Hosseinkhani et al., 2017). Traditional medicinal systems describe certain herbal formulations that have been used for centuries and can be good source for finding possible new drugs for the treatment of PCOS.

6.4 THERAPEUTIC EFFECTS OF SOME HERBAL RESOURCES ON PCOS

6.4.1 Aloe Vera

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Asparagales
Family: Asphodelaceae
Botanical name: *Aloe vera* (L.) Burm. f.

Aloe vera, commonly called as 'Ghrit Kumari' or 'Gwar Patha,' is a succulent plant belonging to family *Asphodelaceae*. It grows mainly in the dry regions of Africa, Asia, and many islands of Western Indian Ocean (Cousins and Witkowski, 2012). It is a perennial herb with thick, fleshy, green leaves with serrated margins. Yellow, tubular, drooping flowers arise in long racemes (Figure 6.3).

6.4.1.1 Major Bioactive Constituents of Aloe Vera

Aloe vera has been reported to yield about 75 different chemical compounds including sugars such as mannose-6-phosphate (monosaccharides), glucomannans, and acemannans (polysaccharides); anthraquinones (aloin, emodin and barbaloin); minerals (copper, zinc, calcium and selenium); vitamins (vitamin A, C, E and B_{12}); enzymes (amylase and catalase); fatty acids (lupeol and campesterol); hormones

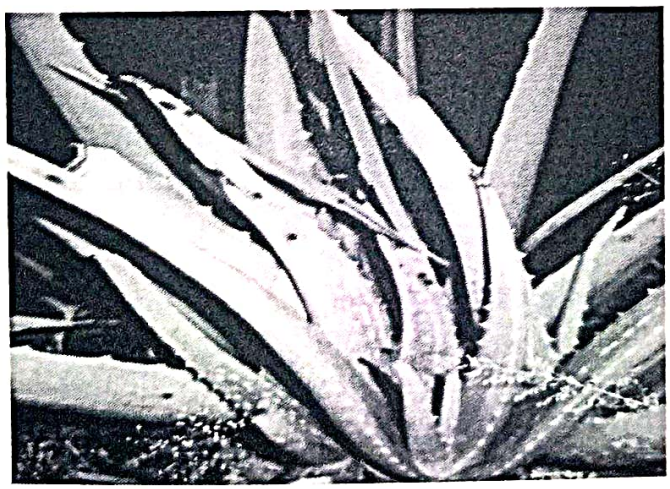


FIGURE 6.3 *Aloe vera.*

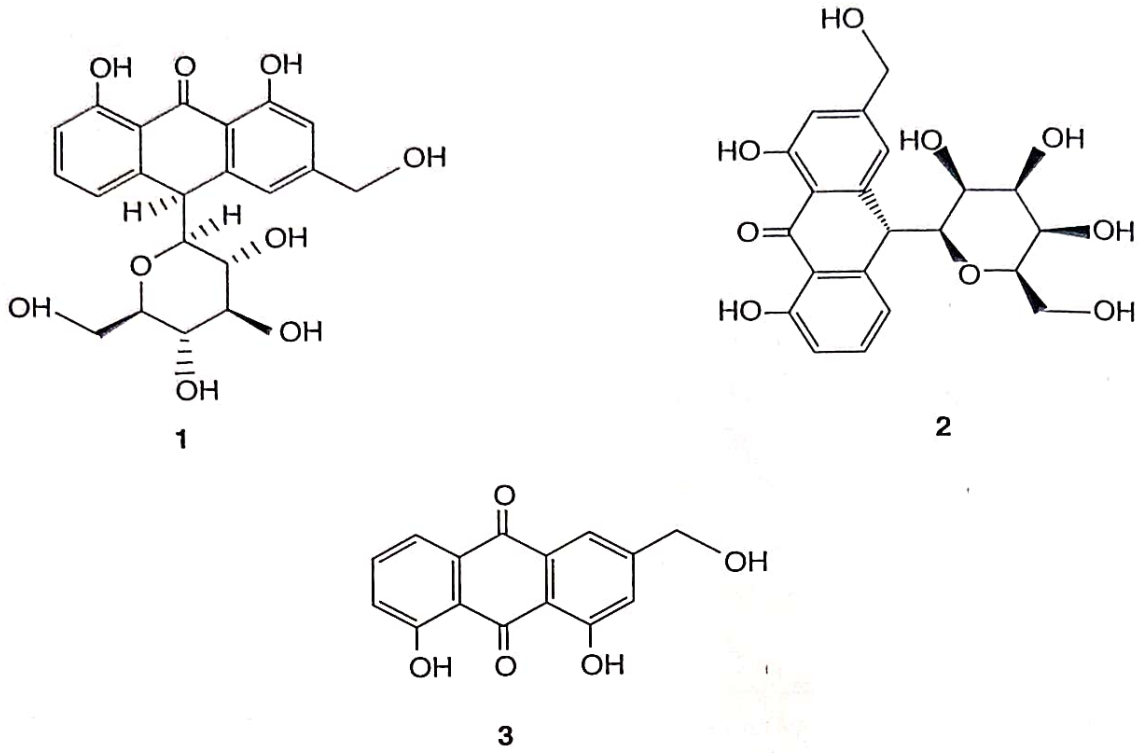


FIGURE 6.4 (1) Alonin, (2) aloe emodin, and (3) barbaloin.

(auxins and gibberellins); lignin, salicylic acid, and saponins (Surjushe et al., 2008; Sanchez et al., 2020). The major bioactive constituents of aloe vera are shown in Figure 6.4.

6.4.1.2 Pharmacological Effects

Aloe vera (L.) Burm. f. has been popularly known for its medicinal effect such as hypoglycemic, lipid lowering, anti-inflammatory, and antioxidant properties (Desai et al., 2012). Its potentially active constituents such as vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, and amino acids possess purgative, antimicrobial, immunostimulatory, wound healing, antitumor, and antidiabetic activities (Hussain et al., 2015). Clinical trial has shown that aloe vera gel dose can improve glucose tolerance in dose-dependent manner, and may cause change in the structure of ovary, and high-dose treatment decreases atretic follicles and 3-beta hydroxy steroid dehydrogenase (3βHSD) and 17βHSD activates. This herb has a hypoglycemic impact and is high in fiber, which has the function of accelerating gastrointestinal transit, absorption, and homeostasis modulation. Aloe vera phytosterols have the ability to modify the steroidogenic response, express estrogen receptor protein, decrease androgen levels, raise estrogen levels, and eventually ameliorate PCOS symptoms. According to certain research, aloe vera can enhance glucose intolerance and lipid metabolizing enzyme activities, lower levels of triglycerides (TG) and low-density lipoprotein, reduce atretic follicles, and diminish atretic follicles (Ashkar et al., 2020). Various clinical/laboratory studies on effect of aloe vera for the treatment of PCOS have been depicted in Table 6.1.

TABLE 6.1
Impact of Aloe vera (*Aloe vera* (L.) Burm. f.) during PCOS-Associated Reproductive Impairments

References	Model	Intervention (Daily Dose)	Duration	Outcome
Maharjan et al. (2010)	5-month-old Charles Foster female rats.	Rats were orally fed with letrozole which urged PCOS in them, then administered orally 1 mL daily dose of aloe vera gel.	45 days	Treatment with aloe vera gel restored estrus cyclicity, maintained normal blood glucose level and reduced androgen level. Aloe vera gel, having phytochemicals such as flavonoids, polyphenols, sterols, has efficacy to prevent the expression of phenotype of PCOS.
Desai et al. (2012)	Charles Foster female rats.	PCOS was induced in rats through oral administration of letrozole at a dose of 0.5 mg/kg body weight. The PCOS positive rats were divided into four groups: 1. PCOS control group 2. Aloe vera gel treated PCOS rats – 1 ml (10 mg)/day for 30 days) 3. PCOS rats treated with metformin 4. positive control group treated with atorvastatin.	30 days	PCOS rats treated with aloe vera gel showed significant reduction in LDL cholesterol levels and plasma triglyceride, and increase in HDL cholesterol. Aloe vera gel also caused reversion of abnormal estrous cyclicity, glucose intolerance and lipid metabolizing enzyme activities, bringing them to normal.
Radha et al. (2014)	Charles Foster adult female rats.	Aloe vera gel fed orally at dose of 5, 10, and 15 mg/kg.	60 days	Treatment with aloe vera gel caused changes to ovarian structure, restored the ovarian steroid status, decreased the insulin resistance, and lowered the testosterone level.

6.4.2 CINNAMON

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Laurales
Family: Lauraceae
Botanical name: *Cinnamomum verum* J. Presl

Cinnamomum verum J. Presl, also known as true cinnamon, belongs to family Lauraceae. It is a small evergreen tree having simple ovate-oblong leaves with smooth margins. Flowers are borne in panicles. Fruit is a drupe having single seed (Figure 6.5).

6.4.2.1 Major Bioactive Constituents of Cinnamon

Leaves – Cinnamaldehyde: 1%–5% Eugenol: 70%–95%
Bark – Cinnamaldehyde: 65%–80% Eugenol: 5%–10%
Root – Camphor: 60%

FIGURE 6.5 *Cinnamomum verum*.

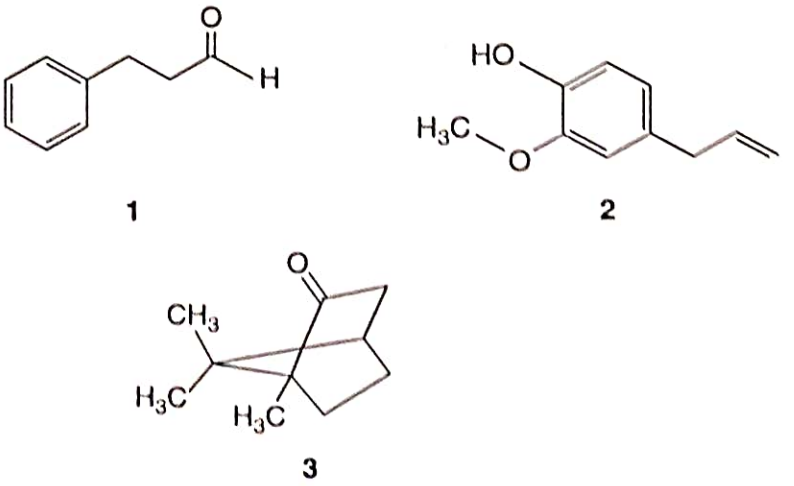


FIGURE 6.6 (1) Cinnamaldehyde, (2) eugenol, and (3) camphor.

Cinnamaldehyde has been shown to increase progesterone and lower androgens such as testosterone and DHEA, thus maintaining the menstrual cycle. Eugenol extracts from essential oil of cinnamon contain antioxidant, anti-inflammatory, antidiabetic, and antiandrogenic properties (Vangalapati et al., 2012). The major bioactive constituents of cinnamon are shown in Figure 6.6.

6.4.2.2 Pharmacological Effects

Cinnamomum verum is an attractive spice because of its aroma and taste and also has several health-promoting effects (Kort and Lobo, 2014). According to a report, taking cinnamon supplements may reduce insulin resistance and enhance the health of PCOS patients (Table 6.2). By acting as a potential therapeutic agent, cinnamon decreases insulin and testosterone levels, lowers insulin-like growth factor-1, and raises insulin-like growth factor-1 (IGF-1) binding protein levels in plasma and the ovary in PCOS (Ashkar et al., 2020). Extracts of cinnamon promote insulin receptor adhesion. It has been discovered to improve the insulin signaling pathway, reduce insulin resistance brought on by high fructose diets, and improve glucose utilization. Additionally, it includes polyphenolic compounds with insulin-like properties such as rutin, catechin, quercetin, and kaempferol (Dou et al., 2018).

TABLE 6.2
Impact of Cinnamon (*Cinnamomum verum* J. Presl) during PCOS-Associated Reproductive Impairments

References	Model	Intervention (Daily Dose)	Duration	Outcome
Wang et al. (2007)	15 women with PCOS (with mean BMI 28.8 ± 1.3 kg/m^2 and mean age 31.1 ± 2.0 years.	Daily 1 g cinnamon extract was given orally to the patients (1 capsule containing 333 mg of cinnamon extract given 3 times per day).	8 weeks	In the cinnamon group, fasting glucose level decreased, HOMA-IR decreased and improved insulin sensitivity.
Borzoei et al. (2017)	84 overweight or obese PCOS patients in the age group of 20–38 years.	Patients in cinnamon group ($n=42$) and placebo group ($n=42$) were administered with 3 cinnamon capsules (each one containing 500 mg).	8 weeks	Treatment with cinnamon improved antioxidant status and serum lipid profile in PCOS patients, increased HDL-C levels and decreased serum level of total cholesterol and LDL-C.

(*Continued*)

TABLE 6.2 (*Continued*)
Impact of Cinnamon (*Cinnamomum verum* J. Presl) during PCOS-Associated Reproductive Impairments

References	Model	Intervention (Daily Dose)	Duration	Outcome
Borzoei et al. (2018)	84 overweight or obese PCOS patients in the age group of 20–38 years.	Patients were administered with cinnamon powder 1.5 g/day (3 cinnamon capsules; each one contained 500 mg).	8 weeks	Administration of cinnamon decreased serum fasting blood glucose, insulin, HOMA-IR (homeostatic model assessment for insulin resistance), total cholesterol, LDL-C and weight, and increased HDL-C.
Dou et al. (2018)	60 Prepubertal C57BL/6 mice (age 25 days)	The mice were randomly divided into three groups (control group, DHEA group and DHEA + cinnamon group). In DHEA + cinnamon group ($n = 25$), the mice were administered with DHEA (6 mg/100 g body weight and cinnamon powder (10 mg/100 g body weight mixed in 100 μL 0.5% methyl cellulose).	20 days	Treatment with cinnamon restores the estrous cyclicity and ovary morphology. It improves insulin sensitivity and reduces insulin resistance, mitigates impaired glucose tolerance, and downregulate/reduce testosterone as well as LH levels.
Khodaeifar et al. (2019)	32 female Wistar rats weighing 200 ± 20 g.	Rats were divided into four groups: G1: control group G2: PCOS group without any therapy G3:rats with PCOS that received a daily oral dose of hydroalcoholic extract of cinnamon (200 mg/kg) for 2 weeks G4: the group with no PCOS but receiving a daily dose of the cinnamon extract (200 mg/kg) for 2 weeks. PCOS was induced by injecting a single dose of estradiol valerate.	14 days	Hydroalcoholic extract of cinnamon can regulate the level of gonadotropin and steroid hormones, decrease the oxidative stress, prevent cystic follicle production, and increase the number of normal follicles.

6.4.3 Fennel

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Apiales
Family: Apiaceae
Botanical name: *Foeniculum vulgare* Mill.

Foeniculum vulgare Mill., commonly called fennel, is an important medicinal and aromatic plant belonging to family Apiaceae. It is indigenous to the shores of Mediterranean sea but widely naturalized in several parts of the world. It is generally cultivated as home yard crop throughout India up to an altitude of 2,000 m (Sood et al., 2012). It is an erect perennial herb with hollow stem and finely dissected feathery leaves. The yellow flowers are borne in terminal compound umbels. Fruit is a dry schizocarp (Figure 6.7).

6.4.3.1 Major Bioactive Constituents of Fennel

Phenols, phenolic glycosides, and volatile aroma compounds such as transanethole, estragole, and fenchone and α-phellandrene have been reported as the major phytoconstituents of this species (Figure 6.8). Phenolic compounds isolated from *F. vulgare* are considered to be responsible for its antioxidant activity while the volatile aroma compounds make it an excellent flavoring agent. Phenolic acids such as 3-O-Caffeoylquinic acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, 1,3-O-di-caffeoylquinic acid, 1,4-O-di-caffeoylquinic acid, 1,5-O-di-caffeoylquinic acid, and flavonoids such as quercetin-3-rutinoside, eriodictyol-7-rutinoside, and rosmarinic acid have been reported to be isolated from *F. vulgare* (Rather et al., 2012).

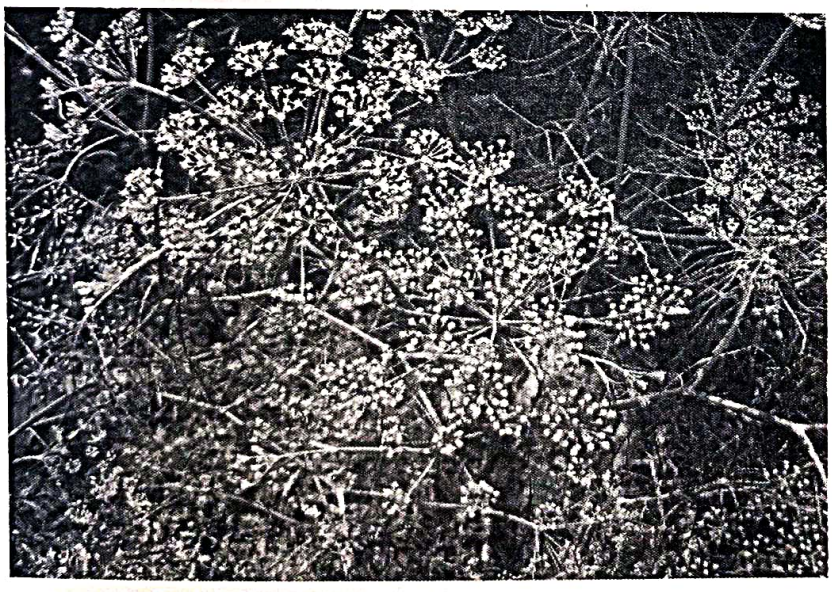


FIGURE 6.7 *Foeniculum vulgare.*

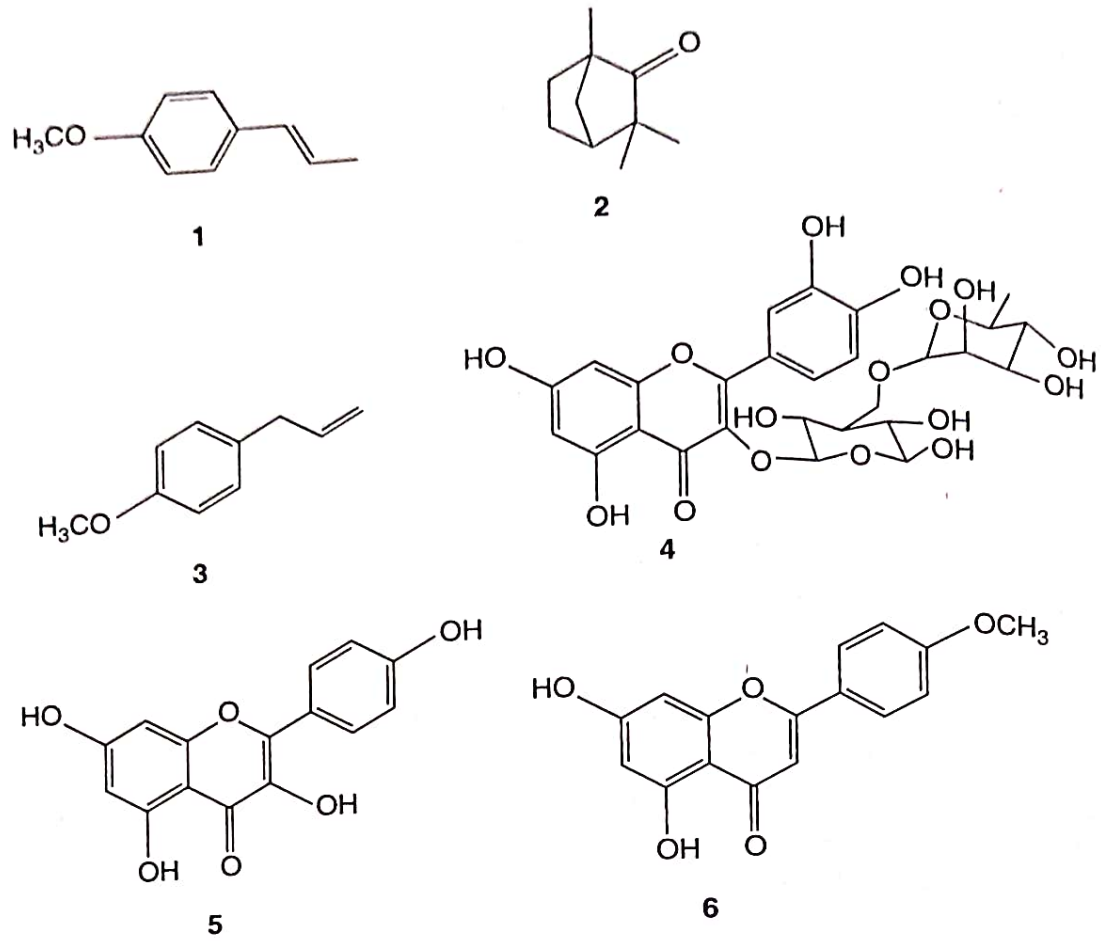


FIGURE 6.8 (1) Trans-anethole, (2) fenchone, (3) estragol, (4) quercetin-3-rutinoside, (5) kaempferol, and (6) acacetin.

Fennel has been reported to exhibit antibacterial, antifungal, hepatoprotective, antiviral, gastroprotective, anthelmintic, antidiabetic, anticancer, memory-protective, estrogenic, antioxidant, antianxiety, and anti-inflammatory properties (Singh, 2019). Extracts of fennel seeds have been shown in animal studies to have a potential use in the treatment of glaucoma, as a diuretic and a potential drug for the treatment of hypertension. Extract of the seeds is used as a galactagogue improving the milk supply of a breast feeding mother (Rather et al., 2012). Different parts of the plant including fruit are used to cure various ailments like mouth ulcer, gum disorders, constipation, conjunctivitis, cold, cough, insomnia, arthritis, diarrhea, fever, liver pain, leucorrhea, and digestive disorders (Badgujar et al., 2014). Anethole, the main constituent of essential oil,, has been reported to be the active estrogenic agent. Aqueous extract of seeds especially at the dose of 150 mg/kg b.w. possessed beneficial effect on renal function in PCOS rats. Phytoestrogen content in fennel is responsible for bringing down insulin resistance and reducing inflammation in PCOS. It has also been reported to reduce the cellular imbalance which leads to metabolic disturbances in PCOS (Sadrefozalayi and Farokhi, 2014; Meena et al., 2019). Various clinical/laboratory studies on effect of fennel for the treatment of PCOS have been depicted in Table 6.3.

TABLE 6.3
Impact of Fennel (*Foeniculum vulgare* Mill.) during PCOS-Associated Reproductive Impairments

References	Model	Intervention	Duration	Outcome
Karampoor et al. (2014)	30 rats with induced PCOS and 6 normal rats as control.	Rats were injected with 2 mL of estradiol valerate. After 60 days, the rats in experiment group were treated with 250, 500, and 1,000 mg/kg of the extract.	60-days administration with estradiol valerate and 10-day treatment with the extract.	Fennel extract increased the serum concentration of FSH and decreased LH and Testosterone in treatment groups.
Sadrefozalayi and Farokhi (2014)	40 adult female Wistar rats (200 ± 20 g).	Dosage: 100, 150 mg/kg/day.	For 4 weeks.	1. Serum urea levels were decreased (only at a dose of 150 mg/kg/day). 2. Histopathology: normal glomerulus, normal basement membrane, and capillaries; Bowman's space (urinary space) and acute tubular necrosis were improved toward normal.
Aliakbari et al. (2022)	70 women with PCOS having age range of 16–40 years.	The intervention group received *B. persicum* capsule (60 mg) + *F. vulgare* capsule (25 mg) twice daily.	4 months.	The treatment of women with PCOS by the combination of fennel and cumin decreased LH and DHEAS levels, hirsutism score and increased menstrual duration.

6.4.4 LIQUORICE

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Fabales
Family: Fabaceae
Botanical name: *Glycyrrhiza glabra* L.

Glycyrrhiza glabra L., commonly known as 'liquorice' belongs to family Fabaceae. It is native to the Mediterranean and certain areas of Asia. It is grown in India, Spain, Iran, Russia, China, and Italy. It is herbaceous perennial plant, with pinnate leaves. The flowers are purple to pale whitish blue in color, produced in a loose inflorescence. The fruit is an oblong pod containing many seeds (Figure 6.9).

6.4.4.1 Major Bioactive Constituents of Liquorice

Liquorice root yields a large number of components including a water soluble complex containing starch, pectins, polysaccharides, simple sugars, amino acids, triterpene, saponin, flavonoids, asparagines, female hormone estrogen, mineral salts, gums, essential oil, fat, resins, tannins, glycosides, protein, sterols, volatile oils, etc. The major bioactive constituents of liquorice are shown in Figure 6.10. Glycyrrhizin, a triterpenoid compound, represents a mixture of potassium–calcium–magnesium salts of glycyrrhizic acid that constitutes 10%–25% of liquorice root extract. Flavonoid-rich fractions include liquirtin, isoliquertin, liquiritigenin, and rhamnoliquirilin. The isoflavones glabridin and hispaglabridins A and B have been reported to possess considerable antioxidant activity (Sharma et al., 2018).

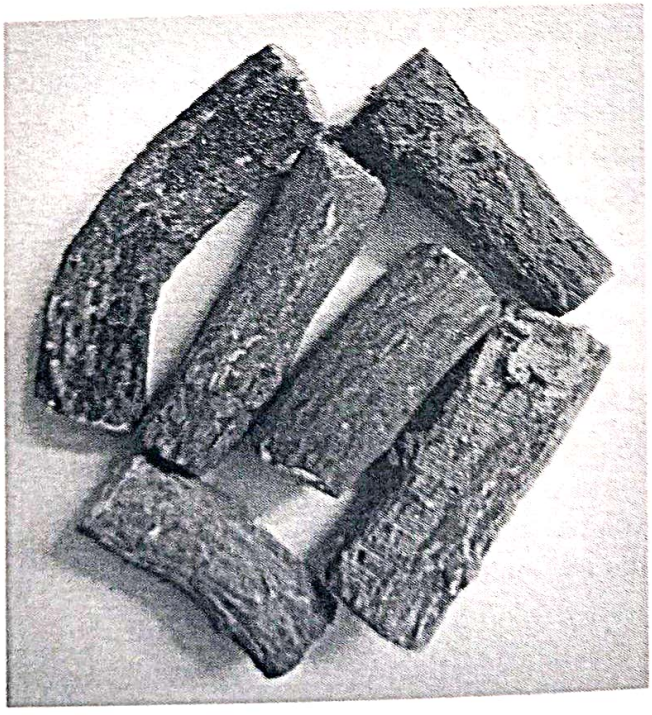


FIGURE 6.9 *Glycyrrhiza glabra.*

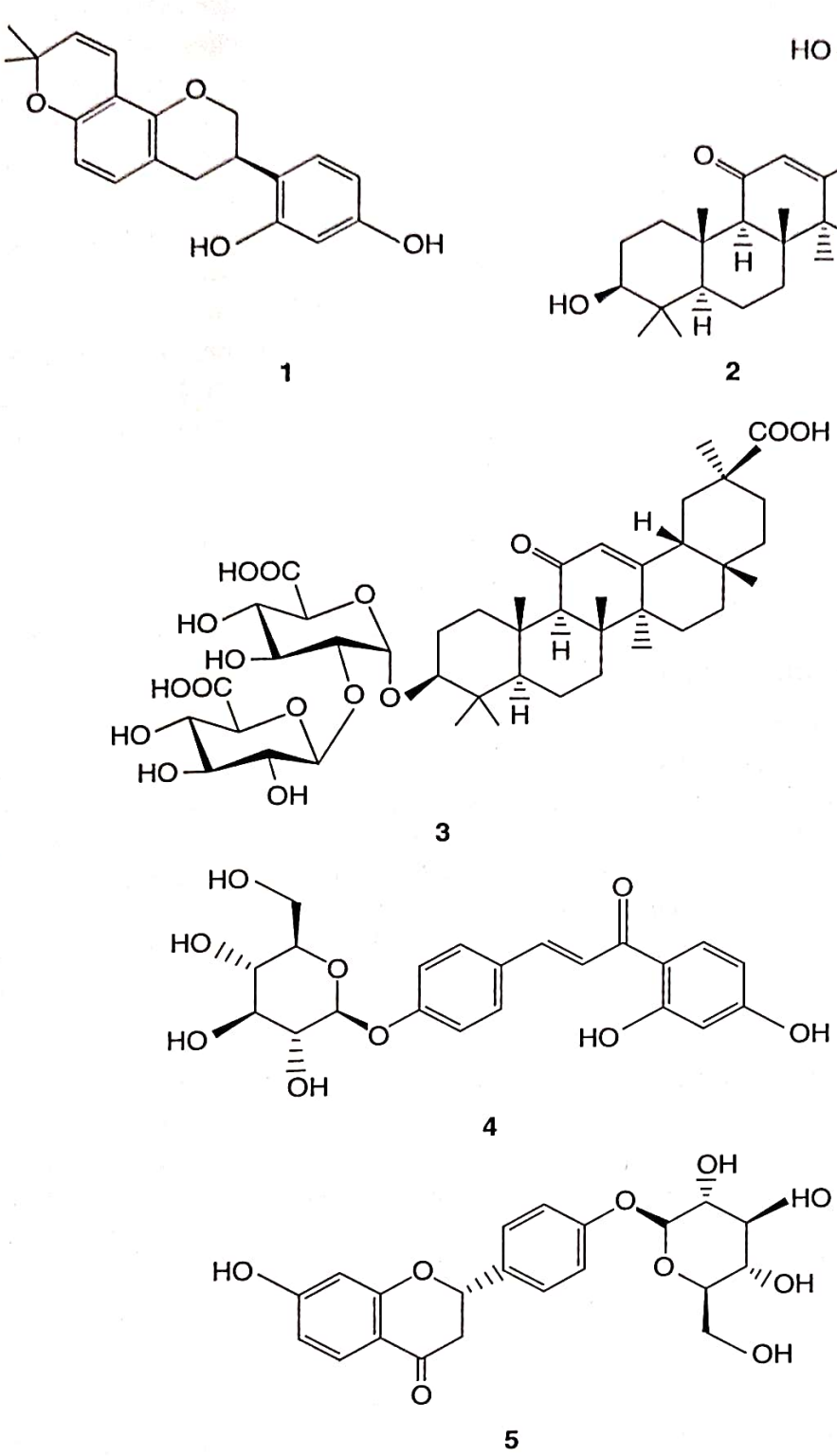


FIGURE 6.10 (1) Glabridin, (2) glycyrrhetic acid, (3) glycyrrhizin, (4) isoliquiritin, and (5) liquiritin.

6.4.4.2 Pharmacological Effects

Liquorice root exhibits multifaceted therapeutic properties such as antimicrobial, antitussive, expectorant, anticoagulant, antiviral, antihyperglycemic/antidiabetic activity, anticarcinogenic, antimutagenic, hepatoprotective, immunomodulator,

antihyperlipidemic, antioxidant, anti-inflammatory, antiulcer activity, and also used to cure throat infection, tuberculosis, respiratory disorders, and liver diseases (Sharma et al., 2018; Wahab et al., 2021). *Glycyrrhiza* roots are useful for treating cough because of its demulcent and expectorant property. It is also used for the treatment of sore throat, anemia, tonsillitis, fever, flatulence, sexual debility, hyperdipsia, skin diseases, swellings, acidity, leucorrhea, bleeding, jaundice, epilepsy, hoarseness, bronchitis, diarrhea, gout, rheumatism, hemorrhagic diseases, and paralysis (Damle, 2014). Administration of liquorice extract leads to the successful elimination of PCOS-associated symptoms, including thinning of the granulosa layer of antral follicles, thickening of the theca layer, reduction in the number of antral follicles, and induction of number of follicular cysts (Kamble et al., 2020). Different clinical/laboratory studies on the effect of liquorice for the treatment of PCOS have been shown in Table 6.4.

TABLE 6.4
Impact of Liquorice (*Glycyrrhiza glabra* L.) during PCOS-Associated Reproductive Impairments

References	Model	Intervention	Duration	Outcome
Armanini et al. (2004)	Nine healthy women aged 22–26 years.	3.5 g of a commercial preparation of liquorice (containing 7.6% w.w. of glycyrrhizic acid) given daily for two cycles.	2 months (two menstrual cycles).	After treatment with *Glycyrrhiza glabra*, total serum testosterone decreased from a mean of 27.8 ± 8.2 ng/dL to 19.0 ± 9.4 ng/dL after one cycle ($p < 0.05$) and to 17.5 ± 6.4 ng/dL after two cycles ($p < 0.05$).
Armanini et al. (2007)	The effect of *Glycyrrhiza glabra* was studied in 32 women with PCOS.	Women with PCOS were divided into two groups: 16 received 100 mg spironolactone and 16 spironolactone plus 3.5 g of liquorice a day.	2 months (two menstrual cycles).	The study demonstrated reduced concentration of testosterone during the first 4 days of treatment at 103 ± 29 ng/day in the spirinolactone group compared to 91 ng/day (± 19) when combined with *Glycyrrhiza glabra* ($p < 0.05$).
Ahmadi and Mostafavi (2015)	Sixty mice divided into six groups.	Hyperandrogenism (HA) was induced by oral administration of 2 mg/kg letrozole. Then effect of liquorice root was studied in three doses: 150, 300, and 450 mg/kg.	21 days.	Improvement of the adverse effects of hyperandrogenism due to PCOS in female mice.

(*Continued*)

TABLE 6.4 (*Continued*)
Impact of Liquorice (*Glycyrrhiza glabra* L.) during PCOS-Associated Reproductive Impairments

References	Model	Intervention	Duration	Outcome
Velvizhi and Annapurani (2017)	30 adult female Wistar rats.	The rats were divided into six groups with 5 rats in each Group I: as control Group II: received 1 mg/kg of letrozole dissolved in 1% carboxy methyl cellulose Group III: received 1 mg/kg b.w. of letrozole along with standard drug Group IV: letrozole for 14 days and then supplemented with *Glycyrrhiza glabra* root extract (100 mg/kg b.w.) Group V: letrozole (1 mg/kg b.w.) in combination with *Glycyrrhiza glabra* root extract (100 mg/kg b.w.) Group VI: *Glycyrrhiza glabra* extract alone.	28 days.	*Glycyrrhiza glabra* root extract with dual antioxidant and anti-inflammatory effects has been reported to be effective in the management of PCOS.
Yang et al. (2018)	Female rats.	Symptoms of PCOS were induced by letrozole treatment for 6-week-old female SD rats, after which the effects of GRR extract on recovery of normal hormonal levels and polycystic ovaries were assessed.	4 weeks.	GRR (Glycyrrhizae radix et rhizome) extract inhibits the symptoms of PCOS by regulating irregular ovarian follicles and imbalanced hormonal levels.
Shamsi et al. (2020)	32 female mice divided into four groups ($n=8$/each).	Group I: control group receiving no treatment Group II: PCOS group injected with estradiol valerate once daily for 21 days. Group III and IV: experimental groups receiving either 100 or 150 mg/kg liquorice, respectively.	21 days.	It has been observed that two doses (100 mg and 150 mg) of liquorice could decrease ovarian cyst and improve the fertilization rate of oocyte and embryo development in PCOS mice.

6.4.5 Pomegranate

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Myrtales
Family: Lythraceae
Botanical name: *Punica granatum* L.

Punica granutam, commonly known as pomegranate (Anar), is a member of family Punicaceae. It is native to Iran and northern India and widely cultivated in the Mediterranean region, Armenia, Iran, India, South Asia, East India, and tropical Africa (Bahmani et al., 2022).

It is a large evergreen shrub or small tree with deciduous, shiny leaves. The flowers are double trumpet-shaped. The fruit is a globose berry with a tough leathery skin (Figure 6.11).

6.4.5.1 Major Bioactive Constituents of Pomegranate

Several chemical constituents have been identified and isolated from different parts of *Punica granatum* such as pericarp, fruit (juice), flowers, leaves, and seeds (Figure 6.12). Polyphenols isolated from *Punica granatum* are hydrolysable tannins including gallotannins, ellagitannins, hydroxycinnamic acids, hydroxybenzoic acids, and gallagyl esters. The major anthocyanins identified in the fruit (juice), arils, and flowers of the plant are cyanidin-3-glucoside, cyanidin 3-rutinoside, cyanidin-3,5-diglucoside, cyanidinpentoside, delfinidin-3-glucoside, delfinidin-3,5-diglucoside, pelargonidin-3-glucoside, and pelargonidin-3,5-diglucoside. Leaves and pericarp contain flavonols and flavones such as catechin, epicatechin, gallocatechin, quercetin, kaempferol, and apigenin. The plant also contains lignans (e.g., dibenzylbutyrolactone, furofuran and dibenzylbutane), minerals (e.g., Ca, Mg, Na, P, K, and N), ursane, oleanane triterpenes (e.g., triterpenic acids), and steroids (Jasuja et al., 2012; Janani et al., 2019; Eghbali et al., 2021).

FIGURE 6.11 *Punica granutam.*

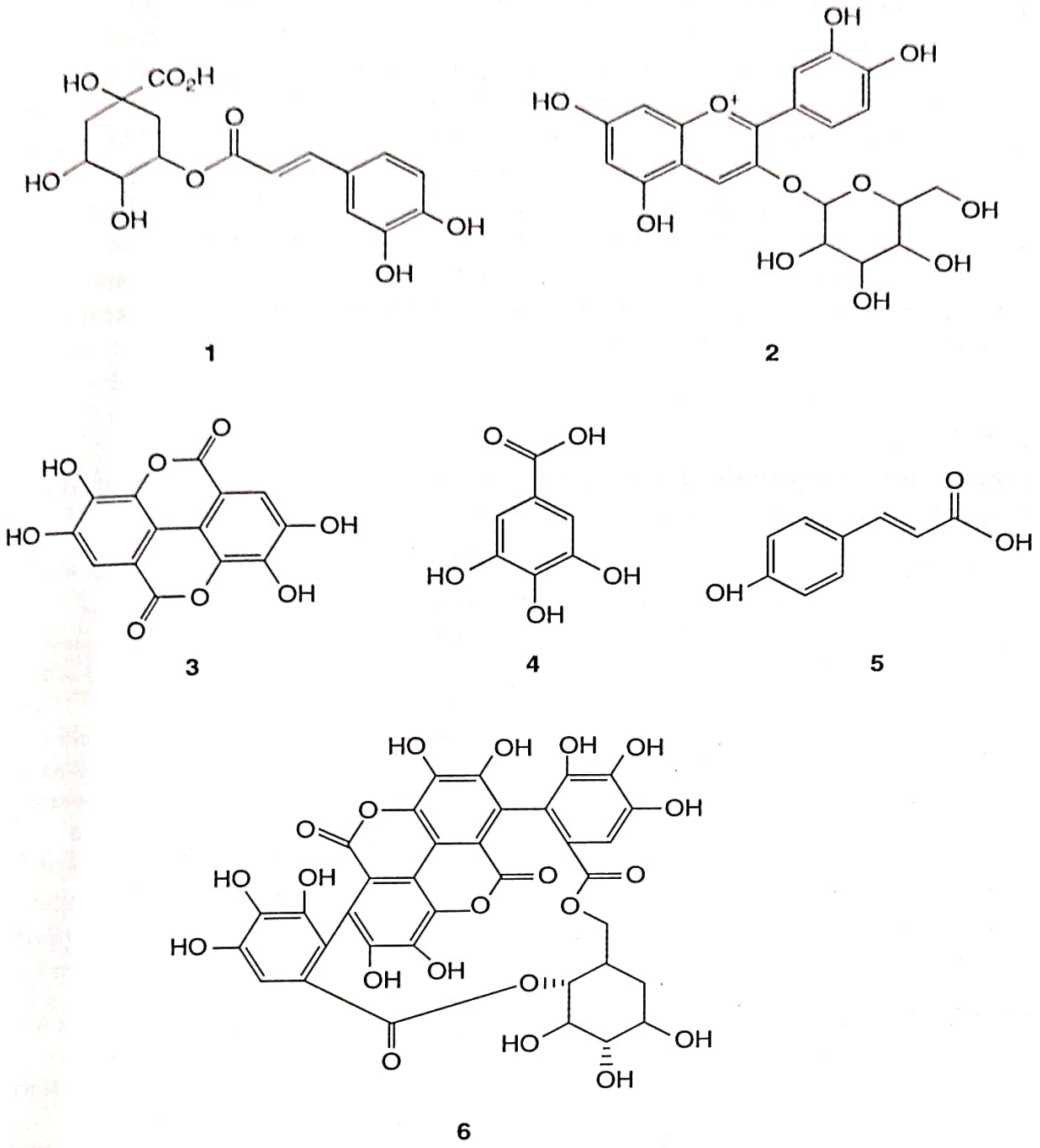


FIGURE 6.12 (1) Chlorogenic acid, (2) cyanidin-3-glucoside, (3) ellagic acid, (4) gallic acid, (5) p-coumaric acid, and (6) punicalin.

6.4.5.2 Pharmacological Effects

In the ayurvedic system of medicine, *Punica granatum* is known as "A pharmacy unto itself" which is used to cure several diseases. Different parts of *Punica granatum* such as bark, leaves, fruit, and fruit rind are used to treat various ailments such as inflammation, obesity, rheumatism, sore throat, male infertility, snakebite, diabetes, diarrhea, burns, Alzheimer's disease, and leprosy. Seeds are used for the prevention of miscarriage (Maphetu et al., 2022). The aqueous extract of peels showed

inhibition of COVID-19 virus replication. The most common use of the plant is as a vermifugal or taenicidal agent, i.e., to kill intestinal worms (Arun and Singh, 2012; Eghbali et al., 2021). The use of plant compounds for pharmaceutical purposes has been gradually increased throughout the world. The extract of plant has been reported to have various therapeutic activities, i.e., antioxidant, antibacterial, antiviral, hepatoprotective, anti-inflammation, antiepileptic, antidiabetic, cardioprotective, and anticarcinogenic activity (Jasuja et al., 2012). The beneficial effect of pomegranate extract on hormonal imbalances of polycystic ovarian syndrome was investigated (Table 6.5) and it has been reported that the phytosterols and phenolic compounds found in the extract have positive effect in improving the complications of PCOS (Hossein et al., 2015).

TABLE 6.5
Impact of Pomegranate (*Punica granatum* L.) during PCOS-Associated Reproductive Impairments

References	Model	Intervention	Duration	Outcome
Hossein et al. (2015)	56 Wistar rats.	The rats were divided into six groups. PCOS was induced in three experimental groups by injecting 4 mg estradiol valerate and then rats were treated with different doses of *P. granatum* extract (100 mg/kg in experimental 1 group, 200 mg/kg in experimental 2 group and 400 mg/kg) in experimental three group.	81 days.	Significant improvement was observed in the levels of testosterone, androsetenedione and estrogen in the treated groups.
Esmaeilinezhad et al. (2019)	92 PCOS patients (triple blinded trial).	Three treatment groups (23 patients each) received 2 l of synbiotic pomegranate juice (SPJ), pomegranate juice (PJ), and synbiotic beverage (SB) weekly. The control group (23 patients) received 2 L of placebo beverage weekly.	8 weeks.	Improvement was observed in insulin resistance, insulin, testosterone level, BMI, weight, and waist circumference in PCOS patients.
Esmaeilinezhad et al. (2020)	Women patients with PCOS (triple blinded trial).	Patients were administered with 300 ml/day of pomegranate juice (PJ), synbiotic pomegranate juice (SPJ) and synbiotic beverage (SB) or placebo beverage (PB).	8 weeks.	Improvement of metabolic, oxidative, inflammatory, and BP consequences in females with PCOS.

6.4.6 Soybean

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Fabales
Family: Fabaceae
Botanical name: *Glycine max* (L.) Merr.

Glycine max also called 'Soybean' belongs to family Fabaceae. It is native to eastern Asia and cultivated throughout the temperate and tropical regions. It is an erect, bushy, herbaceous annual with alternate, compound leaves having two or more leaflets. Flowers are small white to purple-pink in color. Fruit is a hairy pod arising in clusters. Each pod bears 2–4 seeds (Figure 6.13).

6.4.6.1 Major Bioactive Constituents of Soybean

Soybean is rich in isoflavones, a group of plant-derived phenolic compound known as phytoestrogens because of their estrogenic activity. Soybean seeds are the principal source of isoflavones in flavonoid form (Lakshmi et al., 2013). Some major bioactive constituents of Soybean have been depicted in Figure 6.14. There are 12 main isoflavones such as free aglycones, (glycitein, genistein, and daidzein), their respective glucosides (glycitein, genistein, and daidzein), acetyl glucosides (acetylglycitin, acetylgenistin, and acetyldaidzin), and malonyl glucosides (malonylglycitin, malonylgenistin, and malonyldaidzin) in soybean (Riswanto et al., 2021).

6.4.6.2 Pharmacological Effects

By binding to the estrogen receptor, soy isoflavones have the potential to change the activity of steroidogenic enzymes such as p450 aromatase, 3HSD, and 14HSD. The level of testosterone is decreased by blocking the activity of 3HSD, which catalyzes

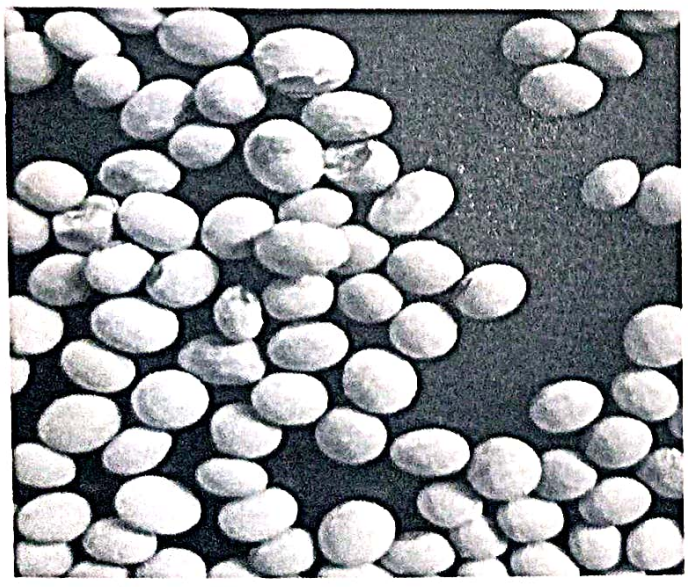
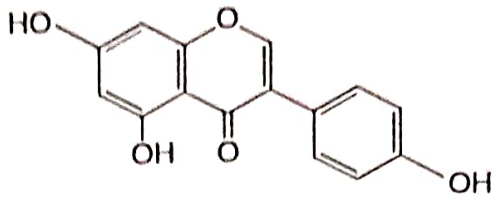


FIGURE 6.13 *Glycine max.*



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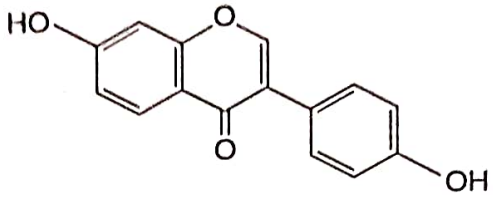

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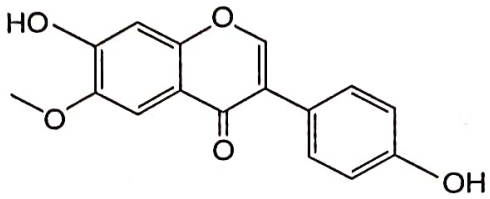

3

FIGURE 6.14 (1) Genistein, (2) daidzein, and (3) glycitein.

the conversion of androstenediol to testosterone (Jamilian and Asemi, 2016). Numerous other health advantages of soy isoflavones, particularly genistein, include a preventive function in cardiovascular illnesses, a reduction in postmenopausal issues, and the prevention of osteoporosis. Daidzein exhibits estrogenic characteristics. A metabolite of daidzein called equol also demonstrated greater estrogenic activity than other isoflavones. Daidzein is therefore distinct from other isoflavones and may be used to treat osteoporosis (Setchell et al., 2002). Histopathological studies indicate the beneficial effect of isoflavones in PCOS (Table 6.6). Isoflavones have been reported to be the natural alternatives as hormonal therapy for menopausal women (Nair and Balakrishnan, 2018).

6.4.7 Spearmint

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Lamiales
Family: Lamiaceae
Botanical name: *Mentha spicata* L.

Mentha spicata also known as Spearmint or Garden Mint is an aromatic perennial herb belonging to family Lamiaceae. Leaves are opposite, toothed along

TABLE 6.6
Impact of Soybean (*Glycine max* (L.) Merr.) during PCOS-Associated Reproductive Impairments

References	Model	Intervention (Daily Dose)	Duration	Outcome
Jamilian and Asemi (2016)	Women diagnosed with PCOS (18–40 years).	70 women randomly allocated to two groups (either administered with 50 mg/day soy isoflavones or placebo).	12 weeks.	Soy isoflavones administration in women with PCOS significantly improved the markers of insulin resistance, hormonal status, TG, and biomarkers of oxidative stress.
Farkhad and Khazali (2019)	32 female Wistar rats divided into four groups ($n=8$).	PCOS was induced by injecting a single dose of estradiol valerate (4 mg/kg) dissolved in 0.2 mL of sesame oil. PCOS rats were treated with soybean isoflavone-aglycone fraction at 50 mg/kg and 100 mg/kg orally once a day.	21 days.	Treatment with soybean isoflavone-aglycone fraction reduced number of cystic follicles and thickness of theca layer. It also improved the total oxidative/antioxidative status.
Ma et al. (2021)	Sprague-Dawley rats.	1 mg/kg letrozole was orally administered for 21 consecutive days to induce PCOS, then soy flavones (100 mg/kg) was administered.	28 days.	Treatment with soy flavones reduced body weight, improved estrous cycle in PCOS rats, decreased serum testosterone and luteinizing hormone level, increased estradiol (E2) and FSH level.

the margins. Stem is square-shaped. Flowers are arranged in terminal spikes (Figure 6.15).

6.4.7.1 Major Bioactive Constituents of Spearmint

Essential oil of spearmint contains 50.6% oxygenated monoterpenes, 45.1% monoterpene hydrocarbons, and 2.8% of sesquiterpene hydrocarbons. The main chemical constituents (Figure 6.16) are limonene, pulegone, cineole, linalool, menthol, carvone, β-pinene, *cis*-dihydrocarvone, dihydrocarveol, piperitone, piperitone oxide, and menthone (Snoussi et al., 2015).

6.4.7.2 Pharmacological Effects

Mentha spicata is used as a carminative, antispasmodic, diuretic, antibacterial, antifungal, and antioxidant agent, and used for the treatment of cold, flu, respiratory tract problems, gastralgia, hemorrhoids, and stomach ache. It is used as

FIGURE 6.15 *Mentha spicata*.

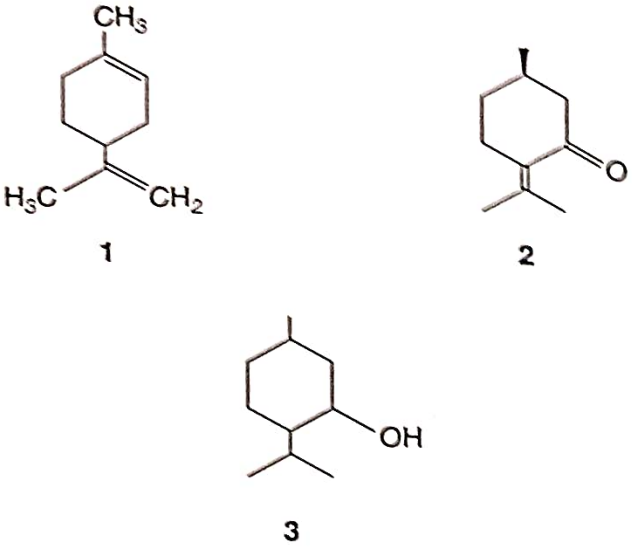

FIGURE 6.16 (1) Limonene, (2) pulegone, and (3) menthol.

folk medicine for bronchitis, nausea, flatulence, liver complaints (Snoussi et al., 2015; Mahboubi, 2021). It has been reported that spearmint tea may be used to treat mild hirsutism in women (Table 6.7). Its antiandrogenic properties reduces the level of free testosterone in blood (Grant, 2010). Spearmint oil containing limonene, pulegone, menthol-like chemical constituents, decreases body weight in the PCOS condition. Its administration leads to decrease of androgen production. Moreover, the spearmint leaf extract's phenolic compounds stimulate the antioxidant defense system and lower the glucose level, body weight, and cholesterol. It induces ovulation and restores follicular maturation in PCOS-induced rats (Attabadi et al., 2017).

TABLE 6.7
Impact of Spearmint (*Mentha spicata* L.) during PCOS-Associated Reproductive Impairments

References	Model	Intervention	Duration	Outcome
Grant (2010)	42 women.	Randomly assigned to drink either placebo herbal tea or spearmint tea twice daily.	30 days.	Spearmint tea group showed significant reduction in free and total testosterone levels as well as the degree of hirsutism and rise in LH and FSH level.
Attabadi et al. (2017)	Female rats.	150 mg/kg spearmint oil or 300 mg/kg spearmint oil.	20 days.	Spearmint oil reduced testosterone level, ovarian cysts, body weight, atretic follicles and increased graafian follicles in rats with PCOS.
Mehraban et al. (2020)	24 rats divided into four groups.	Control (C) group and treatment-control (TC) group received a combination of spearmint extract (SE) and flaxseed extract (FE). After inducing PCOS in PCOS and treatment (T) groups by injecting estradiol valerate, the treatment group received a combination of SE + FE.	30 days.	Significant increase in progesterone and a decrease in testosterone and estradiol with no significant change of DHEA was observed in the treatment group, in comparison with the PCOS group ($p < 0.05$).
Alaee et al. (2021)	Mature Wistar albino female rats divided into six groups ($n = 8$ per group).	Group 1: normal rats Group 2: normal rats + 250 mg/kg spearmint extract Group 3: normal rats + 500 mg/kg spearmint extract Group 4: PCOS-induced rats Group 5: PCOS-induced rats + 250 mg/kg spearmint extract Group 6: PCOS-induced rats + 500 mg/kg spearmint extract.	28 days	Administration of spearmint extract to rats with PCOS resulted in a decreased body weight and testosterone level, higher corpus luteum, and lower ovarian cysts and atretic follicles.

6.5 CONCLUSION

One of the most prevalent female reproductive illnesses is polycystic ovarian syndrome (PCOS). The major goal of PCOS therapies is to restore normal ovarian function such as menstrual cycle regulation, ovulation stimulation, insulin resistance, hyperandrogenism, and PCOS linked to obesity are all treated with medications. Different medications are used to treat PCOS with a variety of symptoms; however, finding an effective cure for PCOS is still difficult. The medicinal plant/herbs (*Aloe vera*, *Cinnamomum verum*, *Foeniculum vulgare*, *Glycine max*, *Glycyrrhiza glabra*, *Mentha spicata*, and *Punica granatum*) have been evaluated and reported to have multiple positive impacts on obesity, polycystic ovarian syndrome, insulin resistance, hyperandrogenism, oligo/amenorrhea, and hyperandrogenism. Therefore, with regard to the increasing prevalence of PCOS, more preclinical and clinical research is needed to examine the efficacy of herbal treatments and for reducing the suffering of women with this fast-spreading endocrine disorder.

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