



## Herbal Products for Gynecological Disorders

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### Abstract

Herbal products are often used as an alternative to pharmacological therapy. Menopausal symptoms and gynecological disorders (such as premenstrual syndrome and dysmenorrhea) are the indications where pharmacological therapy may have serious adverse events; hence many women prefer to use herbal products to help with these symptoms. Here, we reviewed plants and derived products, which are commonly used for the abovementioned indications, focusing on clinical data, safety profile and whether or not their use is justified. We noted that limited data are available on the use of some plants for alleviating the symptoms of menopause and gynecological disorders. While black cohosh (*Cimicifuga racemosa*) and red clover (*Trifolium pretense*) were consistently shown to help reduce menopausal symptoms in clinical studies, currently available data do not fully support the use of fenugreek (*Trigonella foenum-graecum*), hops (*Humulus lupulus*), valerian (*Valeriana officinalis*), and soybean (*Glycine max* and *Glycine soja*) for this indication. For premenstrual syndrome and premenstrual dysphoric disorder, chaste tree (*Vitex agnus-castus*) shows effectiveness, but more clinical studies are needed to confirm such effect upon the use of evening primrose (*Oenothera biennis*).

**Keywords:** Menopause; Dysmenorrhea; Premenstrual syndrome; Gynecological disorders; Herbal products; Medicinal plants.

## Introduction

Women often seek help for various gynecological disorders. Most commonly, these are premenstrual syndrome, dysmenorrhea, and menopausal symptoms. Often, they prefer alleviation of symptoms with herbal products over pharmacological therapy<sup>1</sup>. This is especially the case with, e.g., hormone replacement therapy in menopause, as this therapy bears the possibility for serious adverse events, such as breast cancer<sup>2</sup>. Premenstrual syndrome is characterized by irritability, tension, depressed mood, breast tenderness and bloating in the weeks before menstruation<sup>3</sup>. These symptoms are severe in 5–8% of women. Typical pharmacological therapies include analogues of gonadotropin releasing hormone, estradiol, contraceptives and serotonin reuptake inhibitors. Dysmenorrhea is the occurrence of painful cramps of the uterus<sup>4</sup>. Here, we will focus on primary dysmenorrhea, which is present due to menstruation as opposed to secondary dysmenorrhea, which can have different underlying reasons, such as endometriosis, pelvic inflammatory disease, ovarian cysts, and adenomyosis, to name a few<sup>5</sup>. Typical therapies for primary dysmenorrhea are contraceptives, progestins and non-steroidal anti-inflammatory drugs<sup>4</sup>. Menopause occurs approximately one year after the last menstruation cycle, which stops due to the gradual decrease in ovarian function<sup>6</sup>. The mean age of women entering menopause is 51 years. The transition period, characterized by the cessation of ovarian function, is called perimenopause and starts several years prior to menopause. Women entering perimenopause and menopause experience several symptoms, which are assessed by different criteria. Kupperman menopausal index is often used to measure the intensity of menopausal symptoms (hot flashes, excessive sweating, sleep disturbances, irritability,

depressive mood, attention deficit disorder, joint and bone pain, headache, arrhythmias, paresthesia) assessed on a 1 through 4 scales<sup>7</sup>. Other similar assessments are done with the Greene climacteric scale, or the menopause rating scale<sup>8</sup>. Pharmacological treatments for these symptoms include hormone replacement therapy, selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors<sup>6,9-11</sup>.

## Herbal plants for the treatment of gynecological disorders

### Fenugreek (*Trigonella foenum-graecum* L)

Fenugreek or *Trigonella foenum-graecum* L. is a member of the Fabaceae family. It is grown in the Mediterranean, northern Africa and Indian peninsula to be used as a herb, spice, or in traditional medicine. Fenugreek is an annual plant, which grows up to the height of 60 cm, has trifoliate leaves and white to yellow flowers. Fenugreek seeds grow in thin pods, which are about 15 cm long, and are a part of plant which is commonly used in formulations, such as powder, dry extract or soft extract<sup>12,13</sup>. The seeds are golden yellow and contain polysaccharides (24–25% galactomannans), 0.016% essential oil, 0.6–1.7% saponins (from diosgenin, yamogenin, tigogenin, and others), sterols ( $\beta$ -sitosterol), flavonoids (orientin, isoorientin, isovitexin) and other secondary metabolites (protoalkaloids, trigonelline, choline)<sup>12</sup>. A wide array of versatile compounds contained in fenugreek seeds is the reason that many health effects have been attributed to this plant. These include antidiabetic, antihyperlipidemic, antiobesity, anticancer, anti-inflammatory, antioxidant, antifungal, antibacterial, galactagogue activities, and to help with climacteric and period problems<sup>13</sup>. In this review, we

concentrate on the alleviation of menopausal symptoms and dysmenorrhea.

Diosgenin and yamogenin are steroidal sapogenins, which are obtained after the acid hydrolysis of fenugreek seeds. They are of interest for the pharmaceutical industry due to the possibility to synthesize oral contraceptives and steroid hormone drugs from them, and due to their own pharmacological activity. Another compound with the activity on the endocrine system is the alkaloid trigonelline, which is a phytoestrogen, as it activates the estrogen receptor (ER)<sup>13</sup>. Another set of compounds, which might play a role in alleviating menopausal symptoms and are contained in fenugreek, are flavonoids. Not only trigonelline, but also fenugreek extract showed the ability to bind to ER in a competitive ER binding assay and to have agonist activity on this receptor in a transactivation gene reporter assay<sup>13, 14</sup>. Furthermore, fenugreek extracts upregulated the expression of the estrogen-responsive gene and induced proliferation of estrogen dependent breast cell line MCF-7<sup>14</sup>. Another study showed the antiproliferative effect of fenugreek extract on several breast cancer cell lines, including MCF-7 cells<sup>15</sup>. The same cell line was used for subcutaneous implantation in female mice where diosgenin (which is present in fenugreek seed) inhibited tumor growth<sup>13, 16</sup>. Extract preparation and active compound content may thus be the underlying reason for different results in these studies. Fenugreek extract was shown to improve sexual function in women in a randomized placebo-controlled study, where increased plasma 17 $\beta$ -estradiol was measured, possibly due to increased aromatase conversion of testosterone to 17 $\beta$ -estradiol<sup>13, 17</sup>. In a placebo controlled study on 101 women, fenugreek extract helped with dysmenorrhea symptoms during menstruation<sup>13</sup>. Duration of pain was decreased and reduction of systemic a more than 20% reduction in hot flashes, night sweats, insomnia, and more than 30% improvement of depression<sup>18, 19</sup>. Increases in serum 17 $\beta$ -estradiol, free testosterone and progesterone were observed, and decreases in follicle-stimulating hormone and steroid hormone-binding globulin. Authors speculated that this indicates the phytoestrogenic effect of fenugreek and an establishment of hormonal balance in postmenopausal women upon taking fenugreek extracts<sup>19</sup>. In terms of safety and possible interactions, fenugreek is generally safe, but patients taking antidiabetic drugs should monitor their blood sugar regularly<sup>13</sup>. Fenugreek can cause digestive disorders and allergic reactions<sup>12</sup>. It should not be taken during pregnancy due to uterine stimulatory and abortifacient activities. Moreover, non-clinical data suggest embryo-lethal effects, testicular toxicity and decreased thyroid hormone levels<sup>12</sup> symptoms, such as fatigue, headache and nausea, was observed<sup>20</sup>. A study from 2006, where postmenopausal women were given 6 g of fenugreek seed powder for eight weeks revealed improvement of hot flashes and night sweats after four weeks<sup>21</sup>.

### Hops (*Humulus lupulus* L)

There are three main species in the genus *Humulus* (Cannabaceae): *Humulus lupulus* L., *H. scandens* (Lourr.) Merr. and *H. yunnanensis* Hu.<sup>22</sup> *Humulus lupulus* L. is native to central Europe; however, today it is naturalized throughout the northern temperate regions. It is a perennial and dioecious climbing plant with a herbaceous stem which can reach 10 m. Male small flowers are organized in clusters. The female inflorescences are cones that contain foliaceous bracts and so-called glandular trichomes in the lupulin glands containing essential oil (constituents:  $\beta$ -myrcene,  $\beta$ -caryophyllene,  $\alpha$ -humulene,  $\beta$ -farnesene,  $\alpha$ -selinene,  $\beta$ -selinene, humulene epoxides,  $\beta$ -bisabolol, 2-methyl-3-buten-2-ol, a.s.o.), prenylated acylphloroglucinols ( $\alpha$ -acids: humulone = HU, its derivatives, and  $\beta$ -acids: lupulones), prenylated flavanones

(isoxanthohumol = IX, 6-prenylnaringenin = 6PN, 8-prenylnaringenin = 8PN), chalcones (xanthohumol = XH, desmethylxanthohumol), triterpenes, flavonols, and tannins<sup>23</sup>. XH is the main chalcone in the lupulin glands (0.1–1% of cone dry weight)<sup>24</sup>. Although IX, 6PN and 8PN are present in different varieties of hops<sup>25</sup>, some authors theorized these derivatives could be partly decomposition products emerging during drying and storage<sup>26</sup>. Female inflorescence of hop is important for the production of beer. Moreover, there is a pharmacopoeial drug monograph used for the quality check during the production of herbal teas or herbal preparations (comminuted or powdered herbal drug; liquid extract (DER 1:1), extracted with ethanol 45% v/v; liquid extract (DER 1:10), extracted with sweet wine; tincture (ratio of herbal substance to extraction solvent 1:5), extracted with ethanol 60% v/v; and dry extract (DER 4-5:1), extracted with methanol 50% v/v). They are all mentioned in a category of traditional herbal medicinal products, used for the relief of mild symptoms of mental stress and to aid sleep<sup>27</sup>. Increased interest in therapeutic use of hops dates back to the end of the last century when it was discovered that hops contains prenylflavonoids which are thought to be phytoestrogens. Milligan and colleagues isolated estrogenic 8PN by bioassay-guided fractionation of hops extracts<sup>28</sup>. It has long been traditionally believed that hops has strong estrogenic activity, e.g., in women, harvesting hops by hand, who started menstruating two days after the hops harvesting began. Koch and Heim claimed that the estrogenic activity of hops corresponds to the presence of the equivalent of 20–300 g 17 $\beta$ -estradiol/g<sup>29</sup>.

### Red Clover (*Trifolium pratense* L)

Red clover or *Trifolium pratense* L. is a member of the Fabaceae family. It is native to Europe, Asia and Africa, and has been introduced to every other continent<sup>30</sup>. It is grown in terrestrial and wetlands, and is used for pasturage, hay and silage for the livestock<sup>31</sup>. It is a herbaceous, perennial plant, which grows up to 80 cm tall. The leaves are trifoliate (compounded typically of three leaflets) and alternate. The flowers are pink to red or white in color. Red clover at the flowering stage contains isoflavones formononetin, biochanin A, daidzein and genistein in cumulative concentrations of 5.4–8.1 mg/g of dry matter, where formononetin and biochanin A contribute 51% and 40% of the weight, respectively<sup>32</sup>. Leaves contribute to 73.9% of the total isoflavone content, while stems contribute 17.6% and flowers approximately 9%<sup>32</sup>. In addition, glycitein and prunetin can also be found in red clover in smaller amounts<sup>8</sup>. Isoflavones act as phytoestrogens, as they activate ERs by binding to two isoforms: to estrogen receptor  $\beta$  (ER $\beta$ ) with higher affinity and to estrogen receptor  $\alpha$  (ER $\alpha$ ) with lower affinity<sup>8</sup>. This may, in turn, lead to a reduction of gonadotropin-releasing hormone, follicle-stimulating hormone, and luteinizing hormone levels<sup>33</sup>. Additionally, isoflavones are thought to have antioxidant properties, to inhibit tyrosine kinases, and affect ion transport<sup>8</sup>. Breeding problems of sheep herds in Australia in 1940s, which fed on clover, brought attention to possible hormonal effects of this plant<sup>34</sup>. Many clinical studies were conducted to determine whether red clover could be used to help with menopausal symptoms due to its putative estrogenic activity. A recent (2021) systematic review and meta-analysis by Kanadys et al. presented randomized controlled trials on the use of red clover extract in menopause<sup>8</sup>. The effectiveness of red clover isoflavone extracts on the relief of hot flashes and menopausal symptoms in peri- and postmenopausal women was assessed. Eight trials out of 107 potentially relevant randomized controlled trials passed the quality criteria and were included in comparisons. In most of these trials, 40–80 mg of red clover isoflavone extract was given to participants per day. A meta-analysis revealed a reduction in the hot

flashes frequency, by 1.73 hot flashes per day. The menopausal symptoms were alleviated upon treatment with red clover isoflavone extract according to Kupperman menopausal index and menopause rating scale, but not according to Greene climacteric scale. The red clover isoflavone extract was more effective in women experiencing more than five hot flashes per day, in doses higher than 80 mg of the extract per day, and when the content of biochanin A was higher. Red clover is likely safe when used as a supplement to relieve menopausal symptoms<sup>33</sup>. No significant side effects were seen upon a year of use of such supplements. However, due to its estrogenic activity, patients on hormone replacement therapy or contraceptives, and patients with a history of hormone-dependent cancers should pay special attention to any adverse events. Due to coumarin in red clover, it could have an effect on platelet aggregation; therefore special care is needed if used concomitantly with anticoagulants<sup>34</sup>. Overall, clinical studies support the use of a red clover isoflavone extract for women suffering from menopausal symptoms. Red clover supplements are considered safe for this indication.

### Valerian (*Valeriana officinalis* L)

Valeriana genus (Caprifoliaceae) is comprised of 289 species. The most important one, *Valeriana officinalis* L. (valerian), is known under at least 22 synonyms. It grows naturally in Europe and western Asia, and was introduced to North America. It prefers moist locations, but can also be found in drier soils. Morphology of valerian is very diverse. In the second year of growth, the plant produces a round, furrowed and hollow flowering stem, 80–120 cm tall and branched at the top. The pale green (upper side) lanceolate feathery leaves grow either from one feathered shape or from 9 to 21 finely serrated leaflets. Leaves are attached in pairs to either side of the stem. The stems terminate in umbels bearing many branches and tiny white and pale pink flowers. Valerian has a robust rhizome with many secondary roots and stolons. The European Pharmacopoeia requires as a pharmaceutical material dried, whole or fragmented underground parts of valerian (*Valeriana officinalis* L. s.l.), including rhizome surrounded by the roots and stolons (*Valerianae radix*,<sup>35</sup>) or dried, cut underground parts of valerian, including rhizome, roots and stolons (*Valerianae radix minutata*,). This use in folk medicine has been translated into official therapy, which is confirmed by the existence of a European herbal monograph<sup>36</sup>. Here, we can find indications “for the relief of mild nervous tension and sleep disorders” in the well-established use category, and “for relief of mild symptoms of mental stress and to aid sleep” in the traditional use category. The use of valerian root for nervous disorders during menopause is mentioned only by Usmanghani et al. (1997)<sup>37</sup>.

### Soybean (*Glycine max* (L.) Merr and *Glycine subsp soja* (Siebold & Zucc.) H. Ohashi)

Wild soybean or *Glycine soja* is an annual or perennial climbing herb from the legume family (Fabaceae). It is native in eastern Asia, Russian Far East, eastern China, Korean peninsula and Japan. Wild soybean is not to be mistaken for widely cultivated domesticated soybean or *Glycine max*. In contrast to domesticated soybean, wild soybean has dormant seeds. They are about 1.8–2.5 mm wide, 2.5–4.0 mm long, ellipsoid shape and black in color. Domestic soybean has less genetic diversity and is more susceptible to damage from climatic changes, while wild soybean is more resilient due to 2.8. Soybean (*Glycine max* (L.) Merr. and *Glycine subsp. soja* (Siebold & Zucc.) H. Ohashi) Wild soybean or *Glycine soja* is an annual or perennial climbing herb from the legume family (Fabaceae). It is native in eastern Asia, Russian Far East, eastern China, Korean peninsula and Japan. Wild soybean is not to be mistaken for widely cultivated domesticated soybean

or *Glycine max*. In contrast to domesticated soybean, wild soybean has dormant seeds. They are about 1.8–2.5 mm wide, 2.5–4.0 mm long, ellipsoid shape and black in color<sup>38-41</sup>. Domestic soybean has less genetic diversity and is more susceptible to damage from climatic changes, while wild soybean is more resilient due to its widespread presence in diverse climates and could consequently be a good resource for creating improved genetic variants of domesticated soybean<sup>42</sup>. Wild soybean beans contain a wide range of compounds, among them saponins and isoflavones (e.g., daidzein, 6-hydroxy-daidzein, daidzein glycosides, genistein, genistein glycosides, glycitein, and glycitein glycosides), trypsin inhibitors, and twice the amount of  $\alpha$ -linolenic acid in triglycerides as domesticated soybean<sup>40</sup>. Glycoside forms of the three aglycons may be  $\beta$ -glucosides, 6"-O-malonyl-glucosides and 6"-O-acetyl-glucosides. Isoflavonoid content in domesticated soybean per gram soybeans is up to: 516  $\mu$ g daidzin, 1079  $\mu$ g genistin, 177  $\mu$ g glycitin, 768  $\mu$ g malonyldaidzin, 158  $\mu$ g malonylglycitin, 2446  $\mu$ g malonylgenistin, 265  $\mu$ g genistein. A better absorption was shown for aglycone isoflavonoids than the glycoside forms in humans. Soy isoflavones are of particular interest in the pharmaceutical industry. They mimic estrogen and are thus classified as phytoestrogens, and have antioxidant properties<sup>43-45</sup>. The estrogenic properties of some isoflavones are also the basis for the hypothesis that soy could act as a hormone replacement therapy and thus help alleviate menopausal symptoms. The typical isoflavone ingestion through supplements intended for the relief of menopausal symptoms is 35–150 mg/day. Among soy isoflavones, genistein is the most potent with regard to ER binding, followed by daidzein. Namely, genistein binds to ER $\beta$  with 30 times lower affinity than 17 $\beta$ -estradiol, and to ER $\alpha$  with a 10,000 times lower affinity. This raises a question of whether soy isoflavones could act as selective ER modulators, i.e., exert estrogenic effects in some tissues, but none or antiestrogenic effects in other tissues<sup>44-48</sup>.

### Black Cohosh (*Actaea racemosa* L./*Cimicifuga racemosa* (L.) Nutt)

Black cohosh or *Cimicifuga racemosa* syn. *Actaea racemosa* is a perennial and is endemic to the eastern United States and Canada. This plant belongs to the family Ranunculaceae. It forms up to 2 m of creeping rhizomes. It has elongated fringed divided leaves<sup>49</sup>. Inflorescences of small, white flowers in the form of long clusters appear at the end of branched stems from May to August. The rhizome is used as a herbal drug for medicinal purposes. Native American tribes living in the area of growth of this plant have traditionally used it for centuries<sup>49,50</sup>. Common names for this herb are black cohosh, macrotys, rattle weed and black snake root. In some European countries, the herbal preparations of black cohosh rhizome are marketed as herbal medicines with proven use to relieve menopausal symptoms, e.g., hot flashes. In the United Kingdom, black cohosh is a traditional drug for the symptomatic relief of rheumatic pain<sup>50,51</sup>. There are three groups of compounds in black cohosh that are responsible for its pharmacological action: phenolic compounds, including ferulic acid, isoferulic acid and caffeic acid derivatives, cycloartane triterpene glycosides (actein, 26-deoxyactein) and phenylpropanoids. The phytoestrogenic flavonoid formononetin was also found in early studies of the constituents of this plant<sup>52</sup>, but this was confirmed in neither the raw herb nor the standardized extracts in later studies<sup>49</sup>. Despite numerous research efforts, we do not know the exact composition or function of this plant. The preparations of black cohosh are standardized to the triterpene glycoside content of 26-deoxyactein. Other important triterpene glycosides are actein and cimicifugoside (aglycone cimegenol)<sup>49</sup>. A black cohosh extract contains many triterpene glycosides<sup>53</sup>, but there is no direct evidence that



these are the main active ingredients in relieving menopausal symptoms, especially hot flashes<sup>50</sup>. The efficacy of black cohosh extract in reducing hot flashes may be attributed to the binding and modulation of key central nervous system receptors for thermoregulation, mood, and sleep (e.g., receptors for serotonin, dopamine,  $\gamma$ -aminobutyric acid (GABA),  $\mu$ -opioids). It also affects the improvement of metabolism in the brain and its overall activity<sup>54, 55</sup>. The extract contains active ingredients that act as partial agonists of the serotonin receptors (also known as 5-HT or 5-hydroxytryptamine receptors), which are located in the hypothalamus and are associated with thermoregulation. From the 75% ethanol extract standardized to 5.6% triterpene glycosides, the compound *N*-methyl serotonin was isolated, which could be the main active ingredient of the extract. Another mode of action of the rhizome extract could be via triterpenoids (especially 23-O-acetylshengmanol-3-O-D-xylopyranoside) through modulation of GABA receptors. The triterpenoid deoxyactein has also been associated with beneficial effects in osteoporosis by influencing osteoclast growth and differentiation and mineralization<sup>56, 59</sup>.

### Chaste Tree (*Vitex agnus-castus* L)

Chaste tree or *Vitex agnus-castus* L. is a deciduous shrub or a small tree of the Lamiaceae family, native to areas stretching from the Mediterranean to northern India. It grows to a height of 6 m. It has pale violet panicular inflorescences that ripen into brown fruits with a characteristic, aromatic and peppery aroma<sup>60, 61</sup>. The fruits have been used traditionally for their emmenagogue, lactagogue, vulnerary, carminative, antihelminthic and anti-inflammatory properties<sup>62</sup>, while in terms of rational phytotherapy, they are considered herbal substances most frequently used in the treatment of premenstrual syndrome<sup>61</sup>. *V. agnus-castus* is also believed to have been used by monks as an anaphrodisiac, to diminish their sex drive, hence the common names monk's pepper, chaste tree and chasteberry<sup>61</sup>. Phytochemical compounds of the fruit include volatile compounds (essential oil), flavonoids and other phenolic compounds, iridoids, ketosteroids and diterpenoids<sup>62, 63</sup>. In 2016, an LC/MS method for differentiation between the chaste tree and two related species popular in Japan, *V. rotundifolia* and *V. trifolia*, was described, based on the identification of chastol and epichastol diterpenoids proposed to be marker compounds in chaste tree fruits<sup>64, 65</sup>. According to the European Pharmacopeia<sup>66</sup>, whole, ripe and dried fruits are used as an herbal substance (*Agni casti fructus*). Casticin, also known as vitexicarpin, which is a methoxylated flavonol, is defined to a minimum of 0.08% content in the dried herbal substance. In addition, the extract of chaste trees (*Agni casti fructus extractum siccum*) is prepared from the herbal substance by a suitable procedure using ethanol (40–80%, v/v) and must contain a minimum of 0.1% casticin (dried herbal substance)<sup>66</sup>.

### Evening Primrose (*Oenothera biennis* L)

Evening primrose or *Oenothera biennis* L. is a biennial plant that grows to between 30 and 150 cm in height. It is native to Central America, from where it spread first to North America and Europe. It grows today in regions with a moderate climate all over the world. The plant was named after the pleasant spectacle that unfolds every evening at dusk, when its yellow flowers open. However, they only last until the following day. Fruits are up to 4 cm long and contain numerous small seeds<sup>67, 68</sup>. The plant's stem and leaf juices and poultices were used by Native Americans dermally to treat skin inflammation, bruises and minor wounds, while the leaves were used internally for gastrointestinal disorders and sore throats<sup>69</sup>. Today, the seed oil is well-known, particularly in alternative treatments, for use in inflammatory conditions such as atopic dermatitis, eczema and rheumatoid arthritis, and women's

conditions, which are described in the following sections. The seeds of evening primrose contain approx. 20% of oil (triglycerides), which is yellow to greenish-yellow when unrefined, with a typical odor. Linoleic acid is a highly predominant fatty acid (typically ~70%) followed by  $\gamma$ -linolenic acid (typically ~10%)<sup>67</sup>. Both belong to the group of polyunsaturated omega-6 fatty acids. The European Pharmacopeia specifies limits for individual fatty acids, i.e., palmitic (4–10%), stearic (1–4%), oleic (5–12%), linoleic (65–85%),  $\gamma$ -linolenic (7–14%) and  $\alpha$ -linolenic (max 0.5%) acids, as well as unsaponifiable matter (max. 2.5% determined on 5 g of oil) [34]. Due to the high oxidative instability of the oil, it is important that manufacturers ensure the peroxide value of max. 10.0 (or max. 5.0 if intended for use in parenteral preparations<sup>34</sup>. Regulatory accepted in the European Union is the use of oil obtained from two *Oenothera* species, *O. biennis* L. and *O. lamarckiana* L., in the form of a traditional herbal medicinal product for the symptomatic relief of itching in acute and chronic dry skin conditions, exclusively based upon long-standing use<sup>70</sup>. The mechanism of action of *Oenothera* oil is attributed to the effects of omega-6 fatty acids on immune cells and the synthesis of prostaglandins, cytokines and cytokine mediators<sup>69</sup>. It is also assumed that low levels of prostaglandin E1 in women with premenstrual syndrome lead to increased sensitivity to luteal phase prolactin<sup>71</sup>. Research studies and findings which proposed a possible connection between premenstrual syndrome, prolactin levels, prostaglandins and  $\gamma$ -linolenic acid, an essential fatty acid precursor of prostaglandin E1, originate from the early 1980s<sup>72, 73</sup>, including first clinical studies showing success in the treatment with *Oenothera* oil, for premenstrual syndrome<sup>74</sup> and mastalgia<sup>75</sup>. Data showed that women with premenstrual syndrome have the inability to convert linoleic acid to  $\gamma$ -linolenic acid due to a decreased activity of the delta-6 desaturase enzyme<sup>76, 82</sup>, in addition to hormonal imbalance<sup>71</sup>. Cerin et al.<sup>71</sup> investigated hormonal status (progesterone, estradiol, prolactin, cortisol, aldosterone) and cholesterol, triglyceride, lipoprotein, magnesium and calcium levels, and glucose tolerance in the follicular and luteal phases of the menstrual cycle in women diagnosed with premenstrual syndrome vs. symptom-free controls. The parameters were found to be similar in both groups, except for aldosterone which was lower in the follicular and luteal phases, and cholesterol which was higher in the follicular phase in women with premenstrual syndrome. In the same study, the effect of *Oenothera* oil was also evaluated in a randomized, double-blind crossover design, but no effects were found for any of the biochemical parameters.

### *Commiphora Wightii*

A therapeutic flowering plant known by many common names, including Guggulu, Guggul, and Gugal, *Commiphora wightii* is a member of the Burseraceae family. Although it can also be found in Central Asia, guggul is most frequently found in Northern India. Guggul extract, also known as Gugulipid, is a frequent ingredient in Ayurvedic and herbal remedies. Guggul contains a variety of therapeutic essential oils, gum extracts, and resinous compounds. The study demonstrated that Guggul reduces the DHEA-induced PCOS in the ovarian follicles, which is a key factor in minimizing morphological abnormalities. As a result, the hormonal fluctuations return to normal. The study also shown that the DHEA-induced PCOS profile, which includes the hormones FSH, LH, progesterone, estrogen and testosterone, experienced a sharp rise in hormone levels. Elevated glucose levels were also observed<sup>28</sup>. For the purpose of raising awareness, promoting the use of guggul as a nutritional/dietary supplement, and determining the safety of use in humans, the National Institute of Health Environmental Sciences nominated the Gum Guggul to extract for examination of

the Toxicological parameters and characterization. Gum female reproductiveorgans andhormonal balance<sup>81</sup>. Guggul has been shown to provide advantages for

**Table 1: Commonly used plants in relieving menopausal symptoms**

Plant Species, Drug Part	Active Compounds	Biological Activities/Supposed Mechanism of Action
Black cohosh (Cimicifuga racemosa) rhizome	Phenolic compounds (ferulic acid, isoferulic acid and caffeic acid derivatives, cycloartane triterpene glycosides (actein, 26-deoxyactein, cimicifugoside)) and phenylpropanoids, possibly phytoestrogenic flavonoid formononetin, N $\omega$ -methylserotonin, 23-O-acetylshengmanol-3-O-Dxylopyranoside [52,56,27]	<ul style="list-style-type: none"> <li>• Modulation of key central nervous system receptors for thermoregulation, mood, and sleep (e.g., receptors for serotonin, dopamine, <math>\gamma</math>-aminobutyric acid (GABA), <math>\mu</math>-opioids) [54, 55]</li> <li>• Improvement of metabolism in the brain and its overall activity [54,55]</li> <li>• Modulating osteoclast growth and differentiation and mineralization [58, 59]</li> </ul>
Chaste tree (Vitex agnus-castus) fruit Volatile compounds (essential oil),	flavonoids and other phenolic compounds, iridoids, ketosteroids, chastol and epichastol diterpenoids [62–65] Methoxylated flavonol casticin, (also known as vitexicarpin) [66]	<ul style="list-style-type: none"> <li>• Binding to dopamine receptors followed by a decreased release of prolactin [77,78]</li> <li>• Involvement of serotonergic system has been proposed [79]</li> <li>• Decreased serum prolactin levels [80]</li> </ul>
Evening primrose (Oenothera biennis) seed	20% of oil (triglycerides) containing linoleic acid, $\gamma$ -linolenic acid, palmitic acid, stearic acid, oleic acid, $\alpha$ -linolenic acid, unsaponifiable matter [66,67]	<ul style="list-style-type: none"> <li>• Modulation of the immune response and the synthesis of prostaglandins, cytokines and cytokine mediators [69]</li> </ul>
Fenugreek (Trigonella foenum-graecum) seed	Polysaccharides (24–25% galactomannans), 0.016% essential oil, secondary metabolites (protoalkaloids, trigonelline, choline), 0.6–1.7% saponins (from diosgenin, yamogenin, tigogenin, and others), sterols ( $\beta$ -sitosterol), and flavonoids (orientin, isorientin, isovitexin) [12]	<ul style="list-style-type: none"> <li>• Activation of the estrogen receptor (ER) [13]</li> <li>• Upregulation of the expression of estrogen responsive genes [14]</li> <li>• Proliferation of estrogen-dependent breast cells as well as antiproliferative effect on several cell lines [13-16]</li> <li>• Increased plasma 17<math>\beta</math>-estradiol [13,17,19]</li> <li>• Increased free testosterone and progesterone [19]</li> <li>• Decreased in follicle stimulating hormone and steroid hormone binding globulin [19]</li> </ul>
Hops (Humulus lupulus) inflorescence	Essential oil (constituents: $\beta$ -myrcene, $\beta$ -caryophyllene, $\alpha$ -humulene, $\beta$ -farnesene, $\alpha$ -selinene, $\beta$ -selinene, humulene epoxides, $\beta$ -bisabolol, 2-methyl-3-buten-2-ol, a.s.o.), prenylated acylphloroglucinols ( $\alpha$ -acids: humulone, its derivatives, and $\beta$ -acids: lupulones), prenylated flavanones (isoxanthohumol, 6-prenylnaringenin, 8-prenylnaringenin), chalcones (xanthohumol, desmethylxanthohumol), triterpenes, flavonols, and tannins [23]	<ul style="list-style-type: none"> <li>• Estrogenic effect [28,29]</li> </ul>
Red clover (Trifolium pratense) stem, leaf, flower	Isoflavones formononetin, biochanin A, daidzein and genistein, glycitein and prunetin [8,32]	<ul style="list-style-type: none"> <li>• Activation of the ERs by binding to two isoforms: to estrogen receptor <math>\beta</math> (ER<math>\beta</math>) with higher affinity and to estrogen receptor <math>\alpha</math> (ER<math>\alpha</math>) with lower affinity [8]</li> <li>• Reduction of gonadotropin releasing hormone, follicle stimulating hormone, and luteinizing hormone levels [32]</li> <li>• Antioxidant activity, inhibition of tyrosine kinases and modulation of ion transport [8]</li> </ul>
Soybean (Glycine max and Glycine soja) seed	Saponins and isoflavones (e.g., daidzein, 6-hydroxy-daidzein, daidzein glycosides, genistein, genistein glycosides, glycitein, and glycitein glycosides), trypsin inhibitors, and twice the amount of $\alpha$ -linolenic acid as domesticated soybean [40] Glycoside forms of the three aglycons may be $\beta$ -glucosides, 6 00-O-malonyl-glucosides and 6 00-O-acetyl-glucosides [43]	<ul style="list-style-type: none"> <li>• Estrogenic effect–genistein binds to ER<math>\beta</math> with 30 times lower affinity than 17<math>\beta</math>-estradiol, and to ER<math>\alpha</math> with a 10,000 times lower affinity [44,45]</li> <li>• Antioxidant activity [45]</li> </ul>

## Conclusions

Based on this review, we noted limited data are available on the use of some plants for alleviating the symptoms of menopause and gynecological disorders. While black cohosh and red clover were consistently shown to help reduce menopausal symptoms in clinical studies, currently available data do not fully support the use of fenugreek, hops, valerian, and soybean for this indication. For premenstrual syndrome and premenstrual dysphoric disorder, chaste tree shows effectiveness, but more clinical studies are needed to confirm such effect upon the use of evening primrose.

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