



REVIEW PAPER

Olena Petrivna Sokolik ¹, Galina Olexandrivna Prozorova ²

Current research opportunities for potential phytotherapeutic agents for the treatment of pathologies of the female reproductive system

¹ Department of Pharmacology and Pharmacognosy, Odessa National Medical University, Odessa, Ukraine

² Department of Medical and Biological Disciplines, Pylyp Orlyk International Classical University, Mykolayiv, Ukraine

ABSTRACT

Introduction and aim. Herbal medicine is prescribed for various disorders of the menstrual cycle (uterine bleeding, dysmenorrhea), for the treatment of premenstrual and climacteric syndromes, inflammatory diseases of the genital organs, mastopathy and mastalgia and other pathological conditions. The aim of the study is to analysis and generalization of data from professional literature and own experience in the treatment of patients with pathologies of the female reproductive system by phytotherapeutic methods, taking into account the influence of medicinal plants on various links in the pathogenesis of the disease, as well as making recommendations for improvement and prospects for the use of phytotherapy in the treatment of this pathology.

Material and methods. To make an analysis of literary sources of domestic and foreign authors about usage of medicinal plants for the treatment of pathologies of the female reproductive system.

Analysis of the literature. In the treatment of primary (spasmodic) dysmenorrhea, herbal remedies with an antispasmodic, analgesic, hormone-mimetic effects are prescribed. It can be *Chamomile* (*Matricaria chamomilla* L.), *Achillea millefolium*, commonly known as yarrow, *Viburnum*, Shepherd's purse (*Capsella bursa-pastoris*), *Greater celandine*, *Atropa belladonna*, *Hyoscyamus niger*, commonly known as henbane, black henbane, or stinking nightshade and Abraham's tree. Many plants have bactericidal activity, and this property is used in the treatment of inflammatory diseases of the mucous membranes and skin. Such properties are possessed by flowers of *Chamomile* (*Matricaria chamomilla* L.), *Calendula officinalis*, infusion of Medicinal sage (*Salvia officinalis* L.). For the treatment of functional hyperprolactinemia phytopreparations are also successfully used. It is known that the medicinal plant *Vitex agnus castus* has dopaminergic properties, selectively blocking prolactin synthesis, and reduces follicle stimulating hormone levels. *Strychnos ignatia*, *Caulophyllum thalictroides*, *European cyclamen*, *Lilium tigrinum*, *Iris versicolor* provide a complex effect on the female body, effectively reduces the level of prolactin and the severity of mastalgia, which is confirmed not only by clinical data, but also by mammography data in fibrocystic breast disease. For the treatment of climacteric syndrome, a large number of medicinal plants are used, in particular, the most popular is the *Cimicifuga racemosa*.

Conclusion. The effectiveness of phytotherapeutic drugs has been verified by many clinical trials. Modern phytotherapy is becoming more widespread in clinical practice, as an alternative to drug treatment.

Keywords. climacteric syndromes, female reproductive system, hyperprolactinemia, phytotherapy, premenstrual syndromes

Corresponding author: Olena Petrivna Sokolik, e-mail: sokolikep@gmail.com

Received: 2.12.2021 / Revised: 30.12.2021 / Accepted: 9.01.2022 / Published: 30.03.2022

Sokolik OP, Prozorova GO. *Current research opportunities for potential phytotherapeutic agents for the treatment of pathologies of the female reproductive system.* Eur J Clin Exp Med. 2022;20(1):109–116. doi: 10.15584/ejcem.2022.1.15



Introduction

Dyshormonal disorders are one of the very common functional pathologies of the reproductive system, which occurs in women of different ages. Successful treatment of dyshormonal disorders can restore a woman's reproductive potential and improve her quality of life. The manifestations of dyshormonal disorders are diverse: in young women there are more often cycle disorders, infertility, miscarriage, at an older age – uterine fibroids, endometriosis, chronic pelvic pain.¹ The high frequency of these problems in modern society is associated primarily with the deterioration of environmental conditions, the acceleration of the pace of life, chronic stress, unfavorable diet, work and rest; the role of the characteristics of a woman's reproductive behavior is also important. All this leads to a deterioration in the work of adaptation mechanisms, which leads to the development of dyshormonal disorders of the reproductive system. The manifestation of dyshormonal disorders most often occurs in active reproductive age and is based on subclinical disorders that usually begin during puberty.²

In a complex neuroendocrine system, the main role is played by five links, interacting with each other according to the principle of direct and reverse negative and positive interconnection, which is determined by the nature of the signals coming from the periphery. Physiology and pathology of the menstrual cycle in the clinical aspect most fully reflect the state of the woman's reproductive system. Physiological effects of structures of the highest level of regulation are carried out through nervous and humoral connections. The leading place in these relationships is given to brain neurotransmitters (catecholamines, serotonin, acetylcholine, g-aminobutyric acid, glutamic acid, enkephalins), which are located in extrapyramidal formations. Cerebral neurotransmitters regulate the hypothalamic-pituitary-ovarian level of reproductive function. So, they determine the circadian and circorhythmic rhythms, which are leading in the functioning of the entire reproductive system.³

The second level of regulation of the reproductive system is the hypothalamus. A special role belongs to luteinizing hormone-releasing hormone, follicle-stimulating hormone, and prolactin, and the main role in the regulation of prolactin secretion is assigned to dopaminergic structures. Dopamine inhibits the release of prolactin from the pituitary lactotrophs, and its antagonists (Methyldopa, Reserpine, Chlorpromazine) increase its secretion. The pituitary gland produces gonadotropic hormones – follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which affect the function of peripheral endocrine glands. FSH stimulates the growth and maturation of follicles, secretion of estrogen. The formation and function of the corpus luteum are controlled by the secretion of LH and prolactin.⁴

Depending on the concentration and ratio of sex steroid hormones, the production of the corresponding tropic hormones of the pituitary gland is inhibited or activated. Peripheral endocrine organs (thyroid gland, adrenal glands) are also responsible for the regulation of ovarian function, where complex processes of sex steroid biosynthesis and follicular development take place. The female genitals and mammary glands, as well as the skin, bones and adipose tissue, are target organs with the corresponding regulatory mechanisms.⁵

The hypothalamic-pituitary-ovarian system has versatile adaptive mechanisms that change in the process of maturation, maturity and aging of the body. One of the important periods of a woman's life is reproductive, which is considered as period, intended for conceiving, carrying and feeding a child. In this age range, abortions and their complications, sexual infections, various gynecological diseases, breast diseases, infertility, complications during pregnancy and after childbirth are especially dangerous for a woman's health. The extinction of a woman's reproductive function signals the beginning of the climacteric period, in which premenopause, menopause and postmenopause are conventionally distinguished. It is characterized by a high frequency and severity of symptoms associated with a deficiency of sex hormones, which significantly reduce a woman's quality of life. Often this period is complicated by the development of climacteric syndrome of varying severity with the formation of vegetative-vascular, emotional-mental, metabolic-endocrine disorders and their combination.⁶ The main symptoms of climacteric syndrome are vasomotor and psychovegetative climacteric disorders associated with estrogen deficiency, genitourinary disorders due to atrophy of the lower urinary tract, changes in bone density (osteoporosis). As we know, one of the leading methods of treating menopausal syndrome is hormone replacement therapy. However, not all women are able and willing to start treatment with hormonal drugs.

Throughout the history of medicine, the attention of doctors and scientists is riveted to herbal medicine. Avicenna as one of the founders of medicine, a renowned doctor and scientist, emphasized that there are three main tools of a doctor in medicine: the word, herbs and a knife. It is known that biologically active substances of a plant have much in common in their structure with substances formed in the cells of animals and humans, and therefore preparations based on them are well tolerated and have few contraindications with high efficiency. More and more phytopreparations are being created on the basis of plants. The terms "herbal medicine" and "herbal remedies" were first introduced by the French physician Henri Leclerc, who is rightfully considered the founding father of herbal medicine. He is the author of many books on the use

of medicinal herbs in clinical settings. Modern phytopreparations must meet the following requirements: have a standardized composition; be of impeccable quality, safe; do not contain foreign matter. Therefore, the plants used in the production of phytopreparations are cultivated and processed under strict control. The content and quality of substances in plant raw materials depend on the quality of the soil, climate, fertilizers, moisture content, the time of harvesting the plants, and the quality of processing. It is important that side reactions when taking phytopreparations are 5 times less common than when using others drugs, and the number of contraindications is significant smaller.⁷ In this regard, phytopreparations can be used for a longer time, and when using them, the therapeutic effect occurs more slowly, but is long-lasting.

Phytohormonal preparations have a wide spectrum of action and balanced complex effect on metabolic processes in the body, and are devoid of pronounced side effects. Their influence is realized, first of all, at the cellular level, through the central nervous and endocrine systems. An important aspect of the pharmacodynamics of phytohormones is that they stimulate the function of the endocrine glands as a result of improving the energy supply of endocrine cells and normalizing the synthesis of ribonucleic acid and proteins, without disrupting the physiological hormonal mechanisms of regulation. Thanks to this, the glands continue to function actively at the end of the course of therapy.

Aim

Analysis and generalization of data from professional literature and own experience in the treatment of patients with pathologies of the female reproductive system by phytotherapeutic methods, taking into account the influence of medicinal plants on various links in the pathogenesis of the disease, as well as making recommendations for improvement and prospects for the use of phytotherapy in the treatment of this pathology.

Material and methods

To make an analysis of literary sources of domestic and foreign authors about usage of medicinal plants for the treatment of pathologies of the female reproductive system.

Most analyzed studies were clinical human (70%) and animal studies (30%), and also based on the subject of the papers, most papers on the effects of different plants focused on menstrual irregularities, premenstrual (PMS) and climacteric syndromes, inflammatory diseases of the genital organs, mastopathy and mastodynia (mastalgia), hyperprolactinemia, infertility. Based on time of publication of papers, most of the selected studies were published in the period 2017-2021 and the upward slope of studies has intensified from 2019 to 2021.

Analysis of the literature

The versatility of the action of herbal medicines and the safety of their use make herbal medicine indispensable in gynecology, obstetrics and perinatology, where the fundamental issues are harmlessness to the fetus with a very long duration of treatment, as well as obtaining several effects from a minimum amount of funds. In the overwhelming majority of cases, the body of a pregnant woman and the fetus do not need intensive therapy, but only the prevention of violations of the adaptive-homeostatic reactions of the fetoplacental system. Moreover, such prevention is necessary against the background of treatment of complications of pregnancy and the development of placental insufficiency, with the risk of perinatal infection.⁸

For the treatment of gynecological diseases, plants have also been used for a long time, and now their use in this area has received scientific justification. Herbal medicine is prescribed for various disorders of the menstrual cycle (uterine bleeding, dysmenorrhea), for the treatment of premenstrual and climacteric syndromes, inflammatory diseases of the genital organs, mastopathy and mastalgia and other pathological conditions. In case of menstrual irregularities, ergot alkaloids are used, they are direct-acting regulators of the menstrual cycle. In cases of uterine bleeding, in order to reduce blood loss, ergot preparations (methylergometrine, ergotamine) are used, as hemostatic agents – a decoction or infusion of Stinging Nettle (*Urtica dioica*).⁹ In the treatment of primary (spasmodic) dysmenorrhea, herbal remedies with antispasmodic, analgesic, hormone-mimetic effect are prescribed. It can be *Chamomile* (*Matricaria chamomilla* L.), *Achillea millefolium*, commonly known as yarrow, *Viburnum*, Shepherd's purse (*Capsella bursa-pastoris*), *Greater celandine*, *Atropa belladonna*, *Hyoscyamus niger*, commonly known as henbane, black henbane, or stinking nightshade and Abraham's tree. Many plants have bactericidal activity, and this property is used in the treatment of inflammatory diseases of the mucous membranes and skin. Such properties are possessed by flowers of *Chamomile* (*Matricaria chamomilla* L.), *Calendula officinalis*, infusion of Medicinal sage (*Salvia officinalis* L.).¹⁰

Most often in gynecology, phytopreparations are used in the treatment of menstrual irregularities, premenstrual and climacteric syndromes, inflammatory diseases of the genital organs, mastopathy and mastodynia (mastalgia), hyperprolactinemia and urinary tract diseases. The range of indications for the use of phytopreparations is constantly expanding.

Hyperprolactinemia is one of the common causes of reproductive system dysfunctions, its clinical manifestations are well known: menstrual irregularities, anovulation, corpus luteum dysfunction, amenorrhea,

Table 1. Characterization of compounds identified in medicinal plant

Medicinal plant	Biological active substances	Pharmacological properties
<i>Vitex agnus castus</i>	Protocatechuic (3,4-dihydroxybenzoic) acid, penduletin/eupatorin, luteolin-7-glucoside, isochlorogenic acid a, kaftaric acid, chlorogenic acid, corosol acid, luteolin 1 and 2, vitexin, p-hydroxybenzoic acid, linolenic acid, luteolin glucoside, agnuzide, misodendron, casticin, 6'-o-p-hydroxybenzoylmusaenoside acid, chicory acid, apigenin, artemetin, hydroxy-tetramethoxyflavone, butyric acid	Antioxidant, chemopreventive, immunomodulatory and cytotoxicity, tumoricidal, antimutagenic, antimicrobial, antifungal, insect repellent, larvicidal, fracture healing, osteopenic, antinociceptive, opioidergic, antiepileptic, preventing non-alcoholic fat liver disease and oxidative stress, anti-inflammatory activities
<i>Caulophyllum thalictroides</i>	Magnoflorine, taspine, and boldine are contributed to aporphine alkaloids, quinolizidine alkaloids, triterpenoid saponins, palmitic acid, α -spinasterol, α -spinasterol- β -D-glucopyranoside, stigmasterol, lupeol, cholesterol	Antibacterial activity, anti-inflammatory and analgesic effects, antioxidant effects, antiacetylcholinesterase activity, antitumor activity, inhibitory cytochrome P450, Topoisomerase Inhibitor, Wound Healing,
<i>European cyclamen</i>	Triterpene saponins – isocyclamin and desglucocyclamin I, glycosides, phenolic components, anthocyanin and flavonoids	Antiproliferative activity, cytotoxic, spermicidal, antimicrobial, laxative, abortive, sedative, purgative, emmenagogue and antihelminthic, analgesic, anti-inflammatory, antimicrobial, antioxidative activities
<i>Strychnos ignatia</i>	Vomicine, loganin, mavacurine, novacine, icajine, α -colubrine, β -colubrine, isostrychnine, pseudostrychnine, seudobrucine, 16-hydroxy- β -colubrine, 18-hydroxy-sungucine, 18-hydroxyisosingucine, isobrucine N-oxide, isostrychnine N-oxide, 2-hydroxy-3-methoxystrychnine, cycloartenyl palmitate, fatty acid, proteins, polysaccharides	Inhibition of cyclooxygenase and lipoxygenase, cytotoxicity, anti-cancer activity, xanthine oxidase inhibitory activity, neurotransmitter receptors, antiplasmodial activity, antialcoholic effect and reduction of alcohol induced sleep time, antinociceptive effects, inhibitory effect of CYP450
<i>Lilium tigrinum</i>	Steroidal saponins, polysaccharides (galactose, mannose, arabinose, and galacturonic acid), alkaloids, flavonoids, organic acids	Anti-tumor, hypoglycemic, antibacterial, anti-oxidation, anti-depression, anti-inflammatory
<i>Iris versicolor</i>	(Iso)flavonoids, phenols, fatty acids, terpenoids, steroids, xanthenes, quinones	Antibacterial, antioxidant, anti-inflammatory, anti-cancer, immunomodulatory
<i>Tribulus terrestris</i> L.	Flavonoids (kaempferol, kaempferol-3-glucoside, kaempferol-3-rutinoside, tribuloside, caffeoyl derivatives, quercetin glycosides, rutin), saponins (tigogenin, neotigogenin, gitogenin, neogitogenin, hecogenin, neohecogenin, diosgenin, chlorogenin, ruscogenin, and sarsapogenin), alkaloids, tribulusamides A and B, lignan amides, furostanol glycosides (protodioscin, protogracillin)	Diuretic, aphrodisiac, antiurolithic, immunomodulatory, antidiabetic, absorption enhancing, hypolipidemic, cardiogenic, central nervous system, hepatoprotective, anti-inflammatory, analgesic, antispasmodic, anticancer, antibacterial, antihelminthic, larvicidal, anticariogenic activities
<i>Cimicifuga racemosa</i>	Triterpene glycosides (acetin, cimicifugoside, 27-deoxyacetin), organic acids (isoferulic acid, cimicifugic acids) (A, B, E and F), fukinolic acid, caffeic acid, salicylic acid, cimicifugin, tannins, phytosterin	Labour-inducing effects, hormonal effects (estrogen-like), anti-hyperlipidemia and anti-osteoporosis effects, emmenagogue properties, anovulatory effects, anti-proliferative effects

infertility, galactorrhoea, PMS.¹¹ Hyperprolactinemia is associated with diseases of the mammary glands (cyclic mastodynia, fibrocystic breast disease, galactorrhoea) and menstrual irregularities (secondary amenorrhoea – 60-85%, oligomenorrhoea – 27-50%, hyperpolymenorrhoea due to insufficient function of the corpus luteum, anovulation – 70%), as well as a pituitary tumor. Dopamine agonists are the most commonly used drug in the treatment of hyperprolactinemia. Their 1st generation includes

Bromocriptine (Abergin), Lizurid, Pergolide; II – Quinagolide (Norprolac); III – Cabergoline (Dostinex).¹²

For the treatment of functional hyperprolactinemia phytopreparations are also successfully used. It is known that the medicinal plant *Vitex agnus castus* has dopaminergic properties, selectively blocking prolactin synthesis, and reduces FSH levels. *Vitex agnus-castus*, also called vitex, chaste tree (or chastetree), chasteberry, Abraham's balm, lilac chastetree, or monk's pepper, is a

native of the Mediterranean region. It is one of the few temperate-zone species of *Vitex*, which is on the whole a genus of tropical and sub-tropical flowering plants (table 1). Theophrastus mentioned the shrub several times, as agnos in Enquiry into Plants.¹³ It has been long believed to be an anaphrodisiac, leading to its name as chaste tree, but its effectiveness for such action remains unproven. The preparations of *Vitex agnus castus* are effective in women of different ages with menstrual irregularities associated with hyperprolactinemia and luteal phase insufficiency, is used for mastalgia and PMS, in view of the possibility of a single daily intake, it is convenient for treatment and has a low number of side effects.

Phytopreparations are also used to treat premenstrual and climacteric syndromes.

PMS develops a few days before the onset of menstruation and manifests itself as both mental and somatic symptoms, which are expressed in fear, irritability, mood swings, drowsiness, headache, a feeling of chest swelling, bloating and swelling of the legs. The main hormones that regulate the menstrual cycle throughout a woman's life, as well as the growth and development of the mammary glands, are the hormones of the pituitary gland, ovaries (estrogens and progesterone), thyroid gland, adrenal glands and other biologically active compounds.¹⁴ A large role belongs to prolactin – a hormone produced by the pituitary gland. Prolactin, together with estrogens and progesterone, controls the entire process of mammogenesis, providing both the formation of intraorgan structures and postpartum lactation. The role of prolactin is especially important during pregnancy, when the mammary gland is preparing for lactogenesis. Prolactin provides the synthesis of proteins, carbohydrates and milk lipids. After childbirth, the lactogenic effect of the hormone increases sharply. At the end of lactation, prolactin production drops to baseline. A pathological increase in the level of this hormone outside pregnancy and lactation can cause the development of mastopathy.¹⁵ Often there is not a constant, but the so-called latent increase in the level of prolactin, leading to the development of a symptom complex called PMS (soreness and engorgement of the mammary glands, especially in the second phase of the menstrual cycle or just before menstruation, as well as vegetative disorders, migraine-like headaches, edema extremities, abdominal pain, flatulence). With the onset of menstrual bleeding, all of these symptoms usually disappear.¹⁶

In the pathogenesis of the development of PMS the leading role also is played by the violation of the secretion of serotonin. Serotonin and ovarian hormones have a close reciprocal relationship. Estrogens have a potent modulating effect on monoamine metabolism and central nervous system (CNS) function. The clinical manifestations of premenstrual tension syndrome are associated

with a lack of serotonin in the CNS, relative hyperestrogenism and a violation of the ratio of estrogen and progesterone in the luteal phase of the menstrual cycle.¹⁷

Mastalgia occurs in 45-50% of patients.¹⁸ The most common cause of mastalgia is a disturbance in the estradiol/progesterone relationship and an increase in prolactin secretion. Pain in the mammary glands is observed in 15-30% of women receiving hormone replacement therapy, as well as combined oral contraceptives (COCs), and are observed in the first months of their intake, which is associated with a slight increase in prolactin secretion and its level in blood serum in healthy women.¹⁹

Strychnos ignatia, *Caulophyllum thalictroides*, *European cyclamen*, *Lilium tigrinum*, *Iris versicolor* provide a complex effect on the female body, effectively reduces the level of prolactin and the severity of mastalgia, which is confirmed not only by clinical data, but also by mammography data in fibrocystic breast disease (table 1). *Strychnos ignatia* is a tree in the family *Loganiaceae*, native to the Philippines, particularly in Catbalogan and parts of China.²⁰ The plant was first described by the Moravian (Czech) Jesuit working in the Philippines, brother Georg Kamel who named its seeds “the beans of St. Ignatius”, in honour of the founder of his religious order. *Caulophyllum thalictroides*, the blue cohosh, a species of *Caulophyllum* (family *Berberidaceae*) is a flowering plant in the *Berberidaceae* (barberry) family. It is a medium-tall perennial with blue berry-like fruits and bluish-green foliage. The name cohosh is probably from an Algonquian word meaning “rough”. *Cyclamen purpurascens*, the Alpine, European or purple cyclamen, is a species of flowering plant in the genus *Cyclamen* of the family *Primulaceae*, native to central Europe, northern Italy, and Slovenia. It is an evergreen tuberous perennial with (usually) variegated leaves, and deep pink flowers in summer. *Lilium lancifolium* (syn. *L. tigrinum*) is an Asian species of lily, native to China, Japan, Korea, and the Russian Far East. It is widely planted as an ornamental because of its showy orange-and-black flowers, and sporadically occurs as a garden escapee in North America, particularly the eastern United States including New England, and has made incursions into some southern states such as Georgia.²¹ *Iris versicolor* is also commonly known as the blue flag, harlequin blueflag, larger blue flag, northern blue flag, and poison flag, plus other variations of these names, and in Britain and Ireland as purple iris. It is a species of *Iris* native to North America, in the Eastern United States and Eastern Canada. It is common in sedge meadows, marshes, and along streambanks and shores. The specific epithet *versicolor* means “variously coloured”.²²

Infertility, which occurs in 15-20% of all married couples, should be considered one of the most significant

problems in medicine. It is estimated that approximately 10 million new infertile couples emerge each year. Moreover, in 55-65% of cases, the cause of infertility lies in the woman. Endocrine forms of female infertility are determined primarily by violations of ovulation and account for 35-40% of all forms of infertility. At the same time, 25% of the examined women with infertility of inflammatory genesis have normal hormonal function, and the overwhelming majority (75%) have its disorders. Menstrual cycles are of the type of failure of both phases (35%) or the second phase (45%). Changes in circadian rhythms and folliculogenesis are noted. Herbal preparations containing steroid glycosides (saponins) differ from synthetic hormonal preparations in a balanced complex effect on metabolic processes, due to which there is no violation of the physiological mechanisms of hormone regulation in the body. It is very important that the effect of phytohormones is manifested only against the background of the existing dysfunction of the endocrine glands, without affecting the normally functioning glands. One of the medicines containing steroidal saponins is a herbal preparation derived from the plant *Tribulus terrestris* L. (*Zygophyllaceae*) (Table 1). In terms of the content of furostalone saponins, Tribestan, consisting of n-butanol (n-BuOH) extract of the aerial parts of the plant, exceeds other analogues by 5-30 times. The content in the preparation of protodioscin (the main compound by which Tribestan is standardized) is $\geq 45\%$. *T. terrestris* is a native of the Mediterranean region, widespread in warm regions of Europe, Asia, America, Africa and Australia. *T. terrestris*, known in ancient Greece, is still used in traditional medicine in India, China, Bulgaria and other countries in the treatment of a wide range of diseases, including the urinary tract and sexual dysfunctions. In open clinical trials, *T. terrestris* has shown a positive effect in the treatment of female infertility. Recently, *T. terrestris* herb extract has become one of the most popular herbal products. The drugs based on the saponin fraction of *T. terrestris* are used in the treatment of infertility and libido disorders in men and women.²³

Menopausal syndrome is understood as a set of complaints that women over the age of 45 apply to. The most common disorders are poly- and oligomenorrhea, dysfunctional bleeding, hot flashes, sweating, sleep disturbances, depression. One of the main treatments for menopausal disorders caused by estrogen deficiency is hormone replacement therapy (HRT). However, there are subjective and objective factors that reduce the acceptability of HRT.²⁴ These include contraindications for its implementation, a subjective negative reaction of a woman to taking hormonal drugs, the possibility of side effects, as well as intolerance to certain drugs. Therefore, in recent years, much attention has been paid to alter-

native methods of treating menopausal disorders. Improving health with hot flashes and other complaints of a climacteric nature, protection from osteoporosis without side effects – this is what women in menopause expect from an ideal drug. There has been research in the global pharmaceutical industry for many years to “improve estrogen”, but nature has dealt with it faster. After the so-called selective estrogen receptor modulators (SERMs) have become a sensation in recent years, similar properties have been found in the extract of *Cimicifuga racemosa* (table 1).²⁵ For the treatment of climacteric syndrome, a large number of medicinal plants are used, in particular, the most popular is the *Cimicifuga racemosa* (black cohosh). *C. racemosa* has long been used to treat the effects of snakebites, as a remedy for rheumatism, and later in climacteric syndrome, PMS, and prolonged formation of menstrual function. It has been proven that extracts of *C. racemosa* have a central serotonergic effect (contain components that bind serotonin receptors). There is evidence of the possibility of stimulation of certain substances by *C. racemosa* (estrogen-binding proteins), indirectly suppressing or stimulating estrogen receptors. There is a hypothesis about possible binding with other (not a and not b), not yet identified subtypes of estrogen receptors. The adverse effects caused by *C. racemosa* ranged from mild reactions, such as nausea, vomiting, headaches, dizziness, mastalgia, and weight gain, to acute liver damage, breast cancer metastasis. *C. racemosa* displayed side effects on the liver, cardiovascular, central and peripheral nervous system, gastrointestinal tract.²⁶ The herbal origin of a drug does not automatically mean its safety – it still needs to be proven. Factors that can cause toxicity include misidentification of plant species, different times and locations of collection, incorrect selection of plant parts, improper storage, contamination during preparation, errors in nomenclature and labeling, and falsification. For example, *C. racemosa* has an area of distribution in North America and there are many preparations based on it. In recent years, many drugs have appeared on the market that “use” cheaper species of *Cimicifuga*, which do not have the same effects as *C. racemosa*, despite the differences in chemical composition between them.

There are relatively few medicinal plants available for herbal medicine in this area. Their action can be considered as the action of hormone mimetics. The therapeutic effect of these medicinal plants is due to the still unknown “plant hormones” – substances similar to hormones, but not replacing hormones. Thus, herbal medicines can be effectively used in various obstetric and gynecological pathologies. It should be noted that the advantages of herbal remedies are good tolerance and a small number of contraindications; efficiency comparable to evidence-based medicine therapy.²⁷

Conclusions

The relevance of studying the reproductive health of patients with dyshormonal non-inflammatory pathology of the female reproductive system is due to the steady increase in the share of this pathology in recent years in the structure of gynecological morbidity, the rejuvenation of the patient population, and the lack of a unified algorithm for rehabilitation measures. The choice of adequate tactics for managing such patients from the existing variety of treatment is the key to the success. The effectiveness of phytotherapeutic drugs has been verified by many clinical trials. Since phytopreparations practically do not cause side effects, they can be prescribed for a long time both as an independent treatment and in combination with other drugs. Modern phytotherapy is becoming more widespread in clinical practice, as an alternative to drug treatment. Phytotherapy is not only a scientifically based method of treatment and prevention of diseases, but also a method that has all the rights to creative development.

Declarations

Funding

This research received no external funding.

Author contributions

Conceptualization, O.P.S. and G.O.P.; Methodology, G.O.P.; Software, O.P.S.; Validation, O.P.S.; Formal Analysis, O.P.S.; Investigation, O.P.S. and G.O.P.; Resources, G.O.P.; Data Curation, O.P.S.; Writing – Original Draft Preparation, O.P.S.; Writing – Review & Editing, O.P.S.; Visualization, O.P.S.; Supervision, O.P.S.; Project Administration, G.O.P.; Funding Acquisition, G.O.P.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

References

- Vidal JD. The Impact of Age on the Female Reproductive System. *Toxicol Pathol.* 2017;45(1):206-215.
- Oyola MG, Handa RJ. Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes: sex differences in regulation of stress responsivity. *Stress.* 2017;20(5):476-494.
- Joseph DN, Whirlledge S. Stress and the HPA Axis: Balancing Homeostasis and Fertility. *Int J Mol Sci.* 2017;18(10):2224.
- Ferreira SR, Motta AB. Uterine Function: From Normal to Polycystic Ovarian Syndrome Alterations. *Curr Med Chem.* 2018;25(15):1792-1804.
- Goldsammler M, Merhi Z, Buyuk E. Role of hormonal and inflammatory alterations in obesity-related reproductive dysfunction at the level of the hypothalamic-pituitary-ovarian axis. *Reprod Biol Endocrinol.* 2018;16(1):45.
- Mattina GF, Van Lieshout RJ, Steiner M. Inflammation, depression and cardiovascular disease in women: the role of the immune system across critical reproductive events. *Ther Adv Cardiovasc Dis.* 2019;13:1753944719851950.
- Naseri L, Akbari bazm M, Khazaei M. A Review on Therapeutic Effects of Tribulus terrestris. *J. Med. Plants.* 2019;18(72):1-22.
- Sharifzadeh F, Kashanian M, Koohpayehzadeh J, Rezaian F, Sheikhansari N, Eshraghi N. A comparison between the effects of ginger, pyridoxine (vitamin B6) and placebo for the treatment of the first trimester nausea and vomiting of pregnancy (NVP). *J Matern Fetal Neonatal Med.* 2018;31(19):2509-2514.
- Moini Jazani A, Nasimi Doost Azgomi H, Nasimi Doost Azgomi A, Nasimi Doost Azgomi R. A comprehensive review of clinical studies with herbal medicine on polycystic ovary syndrome (PCOS). *Daru.* 2019;27(2):863-877.
- Della Corte L, Noventa M, Ciebiera M, Magliarditi M, Sleiman Z, Karaman E, Catena U, Salvaggio C, Falzone G, Garzon S. Phytotherapy in endometriosis: an up-to-date review. *J Complement Integr Med.* 2020;17(3). doi: 10.1515/jcim-2019-0084
- Appleton SM. Premenstrual Syndrome: Evidence-based Evaluation and Treatment. *Clin Obstet Gynecol.* 2018;61(1):52-61.
- Verkaik S, Kamperman AM, van Westrhenen R, Schulte PFJ. The treatment of premenstrual syndrome with preparations of Vitex agnus castus: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2017;217(2):150-166.
- Ring M. Women's Health: Polycystic Ovarian Syndrome, Menopause, and Osteoporosis. *Prim Care.* 2017;44(2):377-398.
- Farahmand M, Khalili D, Ramezani Tehrani F, Amin G, Negarandeh R. Effectiveness of Echium amoenum on premenstrual syndrome: a randomized, double-blind, controlled trial. *BMC Complement Med Ther.* 2020;20(1):295.
- Chiaromonte D, Ring M, Locke AB. Integrative Women's Health. *Med Clin North Am.* 2017;101(5):955-975.
- Stute P, Bodmer C, Ehlert U, et al. Interdisciplinary consensus on management of premenstrual disorders in Switzerland. *Gynecol Endocrinol.* 2017;33(5):342-348.
- Iba H, Watanabe T, Motomura S, et al. A Japanese herbal medicine attenuates anxiety-like behavior through GABAA receptor and brain-derived neurotrophic factor expression in a rat model of premenstrual syndrome. *J Pharmacol Sci.* 2021;145(1):140-149.
- Fisher CY, Adams J, Frawley JE, Hickman LD, Sibbritt DW. Is there a role for Western herbal medicine in treating cyclic perimenstrual pain and discomfort? *Aust N Z J Obstet Gynaecol.* 2019;59(1):154-156.
- Morehead A, McInnis LA. Herbal Supplements for Common Women's Health Issues. *Nurs Clin North Am.* 2021;56(1):69-78.

20. He W, Wang P, Chen J, Xie W. Recent progress in the total synthesis of Strychnos alkaloids. *Org Biomol Chem.* 2020;18(6):1046-1056.
21. Sim WS, Choi SI, Jung TD, Cho BY, Choi SH, Park SM, Lee OH. Antioxidant and anti-inflammatory effects of *Lilium lancifolium* bulbs extract. *J Food Biochem.* 2020;44(5):e13176.
22. Hoang L, Beneš F, Fenclová M, et al. Phytochemical Composition and In Vitro Biological Activity of *Iris* spp. (Iridaceae): A New Source of Bioactive Constituents for the Inhibition of Oral Bacterial Biofilms. *Antibiotics (Basel).* 2020;9(7):403.
23. Akbaribazm M, Goodarzi N, Rahimi M. Female infertility and herbal medicine: An overview of the new findings. *Food Sci Nutr.* 2021;9(10):5869-5882.
24. Lee E, Jang M, Lim TG, et al. Selective activation of the estrogen receptor- β by the polysaccharide from *Cynanchum wilfordii* alleviates menopausal syndrome in ovariectomized mice. *Int J Biol Macromol.* 2020;165(Pt A):1029-1037.
25. Wang C, Huang Q, Liang CL, et al. Effect of *cimicifuga racemosa* on menopausal syndrome caused by LHRH-a in breast cancer. *J Ethnopharmacol.* 2019;238:111840.
26. Guo Y, Yin T, Wang X, et al. Traditional uses, phytochemistry, pharmacology and toxicology of the genus *Cimicifuga*: A review. *J Ethnopharmacol.* 2017;209:264-282.
27. Mohsen A, Fatemeh K, Leila N, Mona P, Mohammad Z, Mozafar K. Pharmacological and therapeutic properties of the Red Clover (*Trifolium pratense* L.): an overview of the new finding. *J Tradit Chin Med.* 2021;41(4):642-649.