



MEDICINAL HERBS AFFECTING GONADOTROPIN HORMONES IN WOMEN: AN UPDATED SYSTEMATIC REVIEW

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ABSTRACT

Plants and their derivatives can exacerbate or relieve diseases such as infertility, puberty disorders, and menopause. The present - study examines the role and mechanism of medicinal plants or their products in reducing or increasing the levels of GnRH, FSH and LH in females. The key word "GnRH" or "FSH" or "Luteinizing Hormone" was searched in conjunction with the words Medicinal plant, Herb * and Phyto * in the ISI and PubMed databases (using Endnote software). Then articles related to herbs and products affecting the hormones of GnRH, FSH and LH, were included in the study, following inclusion and exclusion criteria. Plants and plant derivatives that affect fertility disorders and mainly increase GnRH, include *Vitex agnus-castus*, *Thuja occidentalis L.*, *Cimicifuga racemosa*, *Yucca schidigera*, isoflavones and some Chinese herbal compounds. In some cases, plants such as *Emilia coccinea* decrease the fertility of the fetus by lowering the FSH and LH hormones. Also, some herbs and plant compounds are used for disorders and discontinuation of symptoms. These include isoflavones, *Lepidium meyenii*, *Angelica gigas* and Chinese herbal compounds. In some cases, *Radix Ginseng* and isoflavones also cause premature aging and puberty, which this issue should be taken into account for nutritional purposes. Plants and plant compounds, can cause hormonal changes, especially in female GnRH hormones mainly due to presence of having phytoestrogens and by inducing their estrogenic properties.

KEYWORDS: GnRH, female, medicinal herbs, sexual disorders

INTRODUCTION

The medicinal plants are used due to the least side effects and lower prices for the treatment of psychological and physiological diseases¹⁻⁸. Today, despite the existence of multiple treatments to promote different dimensions of health, chemical and herbal treatments are still of particular importance in treating various disorders and diseases⁹⁻¹². The prevalence of infertility among young women in various countries is increasing¹³⁻¹⁶. Chemical treatments and infertility treatments impose a lot of expense on patients as well as trigger many psychological and emotional stress to them and the complications of these therapies may have an adverse effect on the patients' health^{17,18}. The balance of hormones in the body plays a major role in successful pregnancy, or prevents the onset of the reproductive system. The

gonadotropin releasing hormone (GnRH) is one of the hormones that plays an important role in women's reproduction, and the sex hormones (FH) of the Follicle-Stimulating Hormone and (LH) Luteinizing Hormone release from the pituitary gland in response to GnRH¹⁹. These hormones stimulate ovulation and normalize oocyte growth in women²⁰. On the other hand, hormonal disorders also cause symptoms such as hot flashes and other complications in menopause. LH hormone produces less estrogen. Although, the level of FSH still rises after the menopause, eventually the level decreases. Therefore, hormonal balance in this age of menopause is very important^{21,22}. Modulation of these hormones can help in the treatment of infertility and hormonal disorders in women. It also helps in Therapeutic methods including assisted reproductive technology (ART) and treatment of disorders such as polycystic ovary syndrome²³, ovarian hyperstimulation syndrome²⁴ and

hypogonadotropic hypogonadism²⁰. Studies have shown that medicinal herbs can be effective treatments for various diseases, including sexual disorders²⁵. Therefore, due to the increasing use of medicinal plants and the importance of hormonal balance in the treatment of infertility, a systematic study has been conducted to investigate the role and mechanism of medicinal plants or their products in reducing or increasing the levels of GnRH, FSH and LH in female.

METHODS

This systematic study was performed by inserting the keywords in the Endnote software. The key terms were searched in The GnRH, or "FSH" or "Luteinizing Hormone" in combination with the words Medicinal plant, Herb * and Phyto * in the ISI and PubMed Databases. Having identified the available articles and documents, the abstracts of the articles, as well as information from other sources by the researchers, herbs and products that influenced the hormones of GnRH, FSH and LH were selected. Also, merely clinical trials and laboratory studies between 2010 and 2017 were studied and investigated. Articles which did not have full text was not available and those that were not related to the purpose of the study were excluded from the study. Figure 1 illustrates exclusion and inclusion criteria and, studies that meet the inclusion criteria

RESULTS

Plants, herbal derivatives, and herbal formulations shown to be able to induce endocrine function and influence sex hormones in different way. In this study, we reviewed this issue systematically.

Medicinal Plants

Vitex agnus-castus

This plant, which has antioxidant properties and is a phytoestrogen, has been investigated on hypothalamic-pituitary-gonadal axis in experimental mice. The study showed that the gavage of laboratory mice with the extract of this plant can increase the level of LH and FSH hormones. Thus, the Vitex extract enhances the fertility power of old female mice²⁷.

Angelica gigas

This is one of the herbal medicines used in butter. The root powder of this plant regulates the levels of ovarian hormones and possesses anti-osteoporosis

properties. The results of the study indicated that the levels of FSH hormone decreased in the rats that were administered Korean angelica powder, but the serum levels of LH in laboratory rats increased²⁸.

Renshen (Radix Ginseng)

The effect of estrogenic Renshen on reproductive tissues in immature mice was evaluated. Extract of this plant stimulates estrogen biosynthesis and has a negative effect on the level of LH and FSH hormones²⁹.

Emilia coccinea

This plant is used in Africa as a contraceptive. Doses of 1000 and 100 mg / kg / day on mice that were not pregnant were evaluated to determine sexual function and hormonal changes. In this study, high-dose extract reduced the level of FSH and LH in serum without significant changes in estrogen and progesterone levels and ultimately prevented ovulation³⁰.

Thuja occidentalis L. (Cupressaceae)

T. occidentalis are used in various diseases of women, to treat polycystic ovary syndrome (PCOS) in laboratory rats. In this study, the oil of this plant with α -thujone after 21 days of administration has been shown to reduce LH and may be used as an effective treatment (without induction of osteoporosis) in the treatment of PCOS³¹.

Cimicifuga racemosa

It contains phytoestrogens together with clomiphene in women with PCOS lowers LH levels, but does not alter FSH levels. Thus, adding the extract of this plant to clomiphene increases the chances of fertility in women with PCOS by inducing hormonal changes such as increased levels of estradiol and progesterone and increasing the thickness of the endometrium and producing more follicles³².

Yucca schidigera

The addition of this herbal supplement to sheep nutrition increases ovarian response to FSH and, improves folliculogenesis by inducing other cellular changes in the ovaries and thus increases the likelihood of fertility³³.

Lepidium meyenii (Maca)

Maca is used in disabilities and hormonal disorders. Hydroalcoholic extract of this plant in ovariectomized mice resulted in elevated FSH and estradiol levels even at low doses. Therefore, the

plant can be a natural therapeutic choice for postmenopausal women³⁴.

Plant derivative

Isoflavones

Because of these phytoestrogenic properties, Isoflavones in soybean can make a variety of changes to the hormonal system. A study on postmenopausal women showed that supplementation with 70 mg per day of isoflavone after 12 weeks reduced LH levels in women, but did not change levels of FSH, estrone and estradiol³⁵. Exposure of newborn rats to soy isoflavones have increased FSH levels and early exposure to these estrogenic compounds can impair the maturity of these animals³⁶. Genistein is considered as an isoflavone and is a phytoestrogens, which was studied in Bhattarai et al. Its effects on gonadotrophin releasing hormone neurons in young female mice was evaluated. The results showed that this plant phytoestrogen induces GABA and kisspeptin-mediated transmissibility to GnRH neurons with its stimulatory activity on GnRH neurons and thus can increase fertility in laboratory rats.³⁷ Genistein significantly affects the expression of the analyzed estrogen-response genes and reduces the LH and FSH hormones in the rats, which is probably due to the estrogenic properties of the substance as well as the effect on the release of gonadotrophins³⁸. Genistein has dose-dependent effects that increase estradiol in the mean to high dose and reduce both the LH and FSH hormones and thus alleviate the symptoms of abnormal ovarian histomorphology. Hence, Genistein is effective in treating premature ovarian failure and subsequent infertility treatment³⁹. Genistein increases the number of pituitary gonadotropic cells in addition to the changes in the hormones in a way that increase the number of FSH cells (by 21%) and LH cells (by 20%) per mm²⁴⁰. In gilts, exposure to Genistein also leads to changes in endocrine glands, including lowering LH levels after artificial insemination⁴¹. Also, exposure to this plant phytoestrogen during infancy (rats) can disrupt the normal development of the neuroendocrine system and increase serum FSH levels at higher concentrations of the drug but lower LH levels⁴². *Isoflavone daidzein* is one of the other phytoestrogens whose effect on the function of the cells of basic porcine ovarian granulosa and the response to FSH was investigated. The results showed that FSH stimulates the proliferation of ovarian cells and modifies the daidzein of this hormone and thus has a direct effect on ovaries and women's fertility⁴³.

Herbal compounds and formulation

Chinese herbal medicine formula

Combined drugs used in the treatment of infertility may be used with or without acupuncture in traditional Chinese medicine. For example, in a study by Hullender et al.⁴³, a combination of Tao Ren 20% (*Persicae spp. Semen*), Hong Hua 20% (*Carthami spp. Flos*), Chuan Xiong 10% (*Chuanxiong rhizoma*), Shu di Huang 20% (*Rehmannia preparata radix*), Dang Gui 20% (*Angelica sinensis radix*) and Bai Shao 10% (*Paeoniae alba radix*) were used along with acupuncture to treat a patient with diminished ovarian reserve (DOR). The patient's FSH level changed from 14.5 mIU / mL to 8.7 mIU / ml after treatment, and after 3 cycles and more with clomid, the level increased to 16.8 mIU / mL⁴⁴. Lirukang Granule was used with psychotherapy in patients with cyclomastopathy and menoxenia. This combination includes plants such as *Radix Curcumae*, *pseudobarbus Cremstrae seu Pleiones*, *Colla Cornus Cervi* and *Concha Ostreae* at 12 grams per sac. After treatment with this plant, FSH and other sex hormones such as estradiol, progesterone and prolactin increased⁴⁵. In a similar study that investigated the effects of Xiaoyao Pill and Kunbao Pill twice a day on peri-menopausal syndrome and hyperlipidemia, these two plant compounds reduced the level of LH and FSH, thus maintaining hormonal balance in individuals Studied⁴⁶. Su et al. Used *Radix Astragali*, *Radix Angelicae Sinensis*, and *Folium Epimedii* to reduce peri-monosuppression symptoms in rats. After administration of these compounds, estradiol increased in circulation, but the level of FSH decreased. However, changes in LH levels were not observed, and thus this Chinese herbal composition can be used to modulate the sex hormones in the peri-monoplasal syndrome⁴⁷. Shouwu jiangqi is one of the Chinese drug compounds whose effect of extract was studied in Wang et al. on PCOS mice. Extract of *shouwu jiangqi* in high doses with dimethylbiguanide increases the level of FSH but does not change the amount of LH. By altering the plant's composition, this plant Reduces ovarian dysfunction in mice⁴⁸. Acetylshikonin is a plant compound that is a derivative of Zicao (Chinese herbal remedy). Acetylshikonin in laboratory rats reduces LH and FSH levels by inhibiting the secretion or synthesis of these hormones. This is due to its effect on secretion of the exocytosis process of gonadotropic hormone, which leads to infertility in rats⁴⁹. *Yiru Tiaojing* Granule is a Chinese herbal compound consisting of *Rhizoma Curculiginis*

27.2%, *Radix Paeoniae alba* 27.2%, *Radix Morinda officinalis* 22.7%, and *Radix Glycyrrhizae* 22.7%. In the study of the effect of reduction of prolactin *Yiru Tiaojing* Granule, has been shown to affect brain receptors and prevent hyperprolactinemia in rat models. It was also found to increase the levels of LH, estradiol, and progesterone hormones⁵⁰. In a study by Wu et al., a plant compound composed of *Radix Pseudostellariae* 30 g, *Rhizoma Polygonati Odorati* 15 g, *Radices Paeoniae Alba* 12 g, *Eucommia ulmoides* 12 g, *Cornus officinalis* 12 g, *Ligustrum lucidum* 15 g, *Fructus Mume* 12 g, *Semen cuscutae* 15 g, *Radix Pueraria* 10 g and *Radix Trichosanthis* 12 g, *Fructus Lycii* 15 g and *periostracum cicada* 6 g, *Radix Clematidis* 15 g, *Herba Siegesbeckiae* 15 g, *Herba Sarcandrae* 12 g and *Herba Lycopodti* 15 g w *Corydalis Tuber* 12 g, *Finger Citron Fructus Citri Sarcodactylis* 12 g, *Rhodiola dodder* 15 g and *Fructus Mori* 15 g.) To Nourishing yin, supplementing qi, and activating blood were used. Each of These compounds used to address the problem of patients with Primary Sjogren's Syndrome, led to the regulation of reproductive endocrine-immune network. It decreased levels of LH and FSH and regulated other hormones and factors that were elevated abnormally⁵¹. *Bu Shen Tiao Chong* recipe was used to study the molecular pathway in retrieving diminished ovary reserve. This compound consist of medicinal Indian mulberry root (10 g), *Szechuan lovage rhizome* (6 g), Chinese angelica (10 g), mayflower Solomon's seal rhizome (15 g), desertliving *cistanche* (10 g), prepared rehmannia root (15 g), South Dodder seed (15 g), Chinese magnolia vine fruit (6 g), and epimedium herb and fluorite(15 g). It was found that the *Bu Shen Tiao Chong* recipe produces hormones through the equilibrium that it may have a beneficial role in oocyte maturation and repair of the diminished ovary reserve. The plant extract plays this role through the restoring of the depleted brain-derived neurotrophic factor and up regulating the FSH, E2, and Inhibin B hormones⁵². *Radix Astragali*, *Radix Angelicae Sinensis*, and *Folium Epi-medii* are compounds of the medicinal plants used to treat sexual problems. The combination was evaluated for ovariectomized rats and natural aging female rats to determine their safety and efficacy. In this study, it was found that low levels of FSH and LH and other sex hormones were regulated and could be used to treat perimenopausal symptoms. But long-term use of estrogenic effects should be considered⁵³. *QiBaoMeiRan* formula is a combination of *Polygoni Multiflori Radix*, *Angelicae Sinensis Radix*, *Achyranthis Bidentatae*

Radix, Semen Cuscutae, Fructus Lycii, Poria, and Fructus Psoraleae). Due to its phytoestrogenic properties and elevated levels of estradiol decreases the level of FSH and LH in immature rats⁵⁴. The study of Zeng et al.⁵⁵ showed that the use of Chinese herbal combination named Yin, could be effective in decreasing the expression of hypothalamic mTOR mRNA and p-mTOR protein and lowering serum levels of LH and estradiol, thereby delaying maturation of mice. A vivo model of ovariectomized plant compound called Qing'E was studied. This combined powder contains *Eucommniae Cortex* (480 g, beaked with salt), *Psoraleae Fructus* (240 g, beaked with salt), *Juglandis Semen* (150 g), and *Garlic Rhizoma* (120 g, steamed and dried) which, like other compounds, this plant caused elevated levels of estradiol and subsequently LH due to phytoestrogens⁵⁶. Consumption of Chinese Herbs in the following doses of 20g of *Radix Astragali*, 35g of *Radix Rehmanniae Preparata*, 30g of *Cuscuta chinensis Lam*, 35g of *Fructus Ligustri Lucidi*, 30g of *Fructus Psoraleae*, 20g of *Radix Salviae Miltiorrhizae* and 20g of *Rubus idaeus Linn* in combination with other therapeutic methods like Acupuncture can increase the efficiency of these plants. It causes the decrease in the level of FSH and LH in mice with PCOS⁵⁷. Medicinal plants can affect the regulation and modulation of sex hormones in women through binding affinity for estrogen receptors, directly and indirectly by induction of phytoestrogenic properties. Medicinal herbs or their derivatives have several mechanisms for modulating the gonadotropin hormones, as summarized in Fig. 2^{33,52,55}. Figure 1: Flowchart related to the procedure of study of studies. Figure 2: Mechanisms of Effect of Medicinal Herbs and Their Compounds on GnRH Hormonal modulation. Also, medicinal plants can increase estradiol serum levels due to their high estrogenic properties in high doses and in prolonged usage. This is due to the presence of plant phytoestrogens that, with elevated levels of estradiol, result in negative feedback in the hypothalamus, leading to a decrease in GnRH production^{54,58}.

DISCUSSION

The balance of sexual hormones in humans is very important. To produce a successful fertility in the first half of the menstrual cycle, estrogen levels rise and cause the growth and increase of uterine cells. In response to the FSH hormone, an ovum begins to grow inside one of the ovaries. On day of 14 of a 28-day cycle, an ovary is released in response to the

LH hormone. And the increase in progesterone levels occurs in the second half of the menstrual cycle, which results in an increase in the thickness of the lower limb^{32,59}. Therefore, the time taken to use herbal drugs in this interval (the first half of the cycle until the 14th day of a 28-day cycle) is more important for increasing the quantity and quality of oocytes. What should be considered is that in postmenopausal women, levels of LH and FSH levels increase^{60,61}. And the results of the studies may be influenced by confounding factors such as age, weight and lifestyle, and other underlying conditions (such as those that reduce the function of the ovaries)²⁸. Also, poor responder women report weak response to gonadotropins⁶², which should also be considered in plant treatments. Also, soybean isoflavones in animals during puberty or pre-puberty period have adverse effects and disrupt the hormonal balance in these animals. It increases FSH but lowers LH and estradiol levels. These changes, along with other problems, such as down regulation, can cause genes that play a key role in the synthesis of steroid hormones and delay in puberty, which can disrupt the normal functioning of sexual cells^{63,64}. In infancy, due to exposure to phytoestrogens such as Genistein, a disorder occurs in the development of the neuroendocrine system that should be addressed in intake of foods such as soybeans or other herbal supplements⁴². It should

be noted that consuming some plants during fertility can have adverse effects on the fetus or mother and may lead to abortion and teratogenic side effects. On the other hand, some herbs or herbal compounds may lower the LH and FSH hormones and cause other changes in hormones and enzymes⁶⁵; as an example, Plant-derived nutritional supplements can, in addition to the formation of toxicity, reduce the level of LH and FSH hormones and disrupt the hormonal balance⁶⁶. Hence, recognizing plant chemical properties or consulting with a doctor or specialist can be an important step in the treatment of infertility. Plants and plant compounds can cause hormonal changes, especially in female GnRH hormones, mainly due to phytoestrogens and by their estrogenic properties induction. These hormonal changes may be beneficial or harmful based on age, sex life, and type of sexual dysfunction. Therefore, the necessary precautions in this regard should be considered. On the other hand, the dosage and duration of use of medicinal herbs are also considered as two important factors in the effectiveness of natural therapies.

CONFLICT OF INTEREST

Conflict of interest declared none.

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