



Received on 05 May, 2017; received in revised form, 17 November, 2017; accepted, 21 November, 2017; published 01 January, 2018

A SYSTEMATIC REVIEW OF MEDICINAL PLANTS AND PLANT DERIVATIVES AFFECTING INCREASE IN ENDOMETRIAL THICKNESS

Farinaz Farahbod¹ and Saeid Heidari^{*2}

Obstetrics and Gynecology¹, Isfahan University of Medical Sciences, Isfahan, Iran.

Deputy of Research and Technology², Shahrekord University of Medical Sciences, Shahrekord, Iran.

Keywords:

Infertility,
Endometrial thickness,
Medicinal plants, herbal therapy

Correspondence to Author:

Saeid Heidari Soureshjani

Deputy of Research and Technology,
Social Determinants of Health
Research Center, Shahrekord
University of Medical Sciences,
Shahrekord, Iran.

E-mail: heidari_1983@yahoo.com

ABSTRACT: Endometrial thickness is one of the determinant factors in fertility success. This study was carried out to determine the effects of plants on increasing endometrial thickness and ultimately increasing fertility preservation. Key terms of "endometrium thickness" or "endometrial thickness" or "endometrial lining thickness" in combination with the words "Medicinal plant", "Herb" and "Phyto" were searched on the ISI, PubMed and Scopus databases. Then, the abstracts of the articles, as well as information obtained from other sources about medicinal plants and their derivatives from which their effects directly on endometrial thickness and pregnancy were studied, were selected. Besides, only clinical trials and laboratory studies between 2007 and 2017 were included. The results from this study showed that plants such as *Cimicifuga racemosa* and *Aspalathus lineararis* and plant derivatives such as Klimadynon and Icarin and plant formulations such as Xiaoyao powder, Erzhi pill and Siwu decoction can increase fertility in humans or animals by increasing endometrial thickness. Medicinal plants and their derivatives affect the thickness of the endometrium, mainly due to having phytoestrogen and can help maintain the fetus in the uterus and increase fertility preservation. The phytoestrogens available in plants are bound to ER- α receptors and mimics the function of estrogen. However, the effective dose, administration time, endogenous estrogen status and type of herbal prescription or derivatives are of important factors that should be considered in herbal therapy.

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.

One of the important factors in the success of pregnancy is the thickness of the endometrium (ET) and then in the thickness of $6 < ET \leq 10$ mm, there is the most likelihood of pregnancy¹³. Experts in the methods of "assisted reproductive technology (ART)" considered this issue, since successful implantation and increased fertility chances depends on achieving the appropriate endometrial thickness in women undergoing treatment¹⁴⁻¹⁶.

In some cases infertility therapists do not care about infertility treatments, thus therapeutic approaches should be adopted for it¹⁷. As the low thickness of the endometrium causes problems in endometrial glandular growth and angiogenesis,

	QUICK RESPONSE CODE DOI: 10.13040/IJPSR.0975-8232.9(1).53-57
	Article can be accessed online on: www.ijpsr.com
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(1).53-57	

and by doing these changes, the vascular endothelial growth factor (VEGF) is reduced. In other words, the implantation and vascularization are weaker than the effects of low endometrial thickness, which causes early abortion¹⁵.

Estrogen therapy is used as one of the effective factors in the treatment of low endometrial thickness without disorder in folliculogenesis and ovulation¹⁸. Estrogen is received by estrogen receptor alpha (ER- α), and estrogen prevents endometrial tissue atrophy and helps to grow and increase its thickness¹⁹⁻²².

In plants, there are also estrogenic compounds that have a function similar to that of androgen in the body. Phytoestrogens available in plants as safe plant compounds can be used to treat low endometrial thickness. Considering that herbs and natural compounds can be effective treatments for various diseases, including infertility¹⁷⁻²⁷, and regarding to the low side effects and cost herbal treatments, in this review study, we aimed to review the effect of plants on increasing endometrial thickness and ultimately increasing fertility.

METHODS: This systematic review was carried out based on the search of the key words of interest. The key words were "endometrium thickness" or "endometrial thickness" or "endometrial lining thickness" as well as the words "Medicinal plant", "Herb" and Phyto* in the ISI, PubMed and Scopus databases. To search for the resources in the ISI databases and PubMed, the Endnote software was used, and to search in Scopus, its database was searched for.

Having identified existing articles and documents, abstracts of the articles as well as information obtained from other sources about medicinal plants and their derivate affecting directly on endometrial thickness and pregnancy were studied, selected and examined. Besides, only clinical trials and laboratory studies between 2007 and 2017 were examined. No full text articles and resources, review articles, studies with no positive effects, non-English language studies, and articles that were not relevant to the purpose of the study were excluded from this study. **Fig. 1** illustrates inclusion and exclusion criteria in this study.

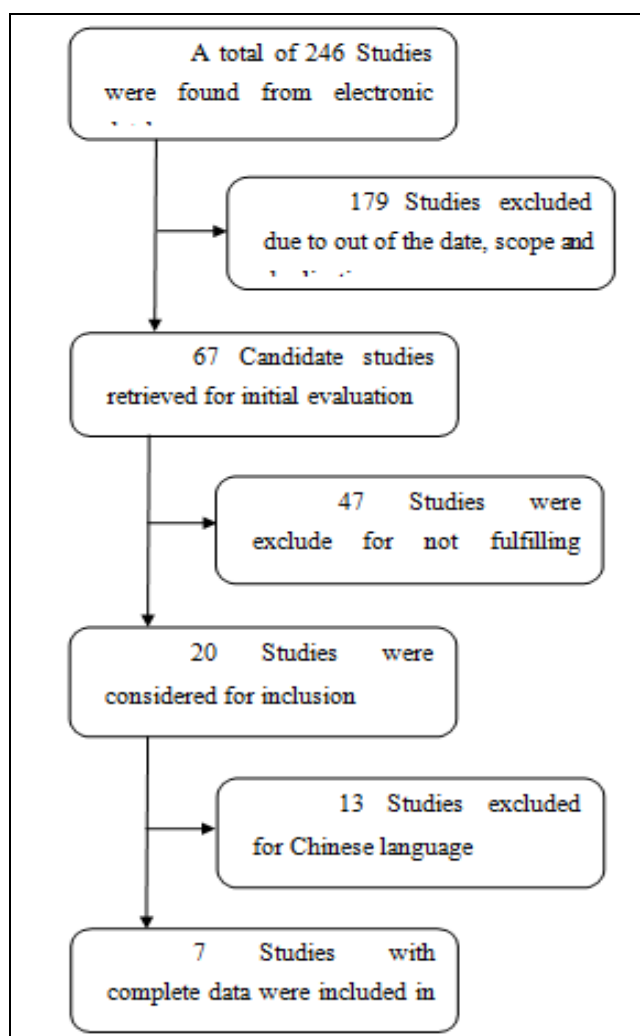


FIG. 1: FLOWCHART OF STUDY SELECTION OF PROSPECTIVE STUDIES

RESULTS:

Medicinal Plants:

***Cimicifuga racemosa*:** This plant is a member of the buttercup family with phytoestrogenic compound and is used to reduce menopausal complications. In a study, it was found that adding this plant to clomiphene could increase endometrial thickness and other factors affecting fertility in women with PCOS²⁸.

***Aspalathus linearis*:** This plant, also known as rooibos, grows in African countries. In a study, the effects of this plant on reproductive system of female rats and its effect on kidney and liver function of these animals were investigated. Rooibos increased the thickness of the endometrium without inflammation, while the myometrium was unchanged. In this way, this plant increased fertility in mice²⁹.

Plant Derivatives:

Klimadynon: *Cimicifuga racemosa* is a plant that has estrogen properties and is used to treat menopausal symptoms. Klimadynon is one of the plant compounds derived from this plant. In a study by Kamel on the herbal extracts on women with PCOS, it showed that this phytoestrogenic composition by regulating sexual hormones and increasing endometrial thickness could increase fertility in women³⁰.

Icariin: It is a phytoestrogenic active compound that affects estrogen receptors. In a study that examined this compound on a thin endometrium of female rats for 6 - 8 weeks, it was found that this combination was effective in increasing the thickness of the endometrial tissue by modifying VEGF, CD31 and factor VIII³¹.

Plant Formulations and Formulations:

Xiaoyao Powder: This powder includes plants such as *Chaihu (Radix bupleuri chinensis)* 15 g, *Baizhu (Rhizoma atractylodis macrocephalae)* 15g, *Baishao (Radix paeoniae alba)* 15 g, *Dagguai (Radix angelicae sinensis)* 15 g, *Shengjiang (Rhizoma zingiberis recens)* 6 g, *Fuling (Poria)* 15 g *Gancao (Radix glycyrrhizae)* 6 g and *Bohe (Herba menthae haplocalycis)* 6 g, which has been studied on 30 women with tubular infertility with GnRHa / FSH / hCG therapy. In this study, it was shown that the aforementioned combination can help to increase fertility by increasing expression of GDF-9 in granulosa cells³².

Erzhi Pilland Siwu Decoction: The two herbal compounds regulate gastrointestinal problems, anxiety, and anger and sleep in patients. Besides, in a study, these two herbs were used to increase fertility, fertilization, and fetal fertilization in the treatment of infertility. The herbal compounds were tested on 42 patients. In this study, in addition to increasing fertility and embryo quality in the experimental group, endometrial thickness was significantly increased compared to the control group³³. Estrogen increases endometrial thickness by affecting glands and endometrial cells and increasing the blood flow of the functional layer. Besides, in plants, phytoestrogens can also increase endometrial thickness by imitating estrogens functions and binding to alpha-type estrogen receptor (ER- α)³⁴.

Therefore, a competition between estrogens and phytoestrogen is attributed to estrogen receptors, and in addition to estrogenic properties, anti-estrogenic properties of plants on reproductive system can also be observed³⁴. In general, phytoestrogens do not appear to have strong phytoestrogenic properties, and even their application does not show adverse and anti-estrogenic effects in cases where the endometrial thickness is normal²⁹.

Phytoestrogens (such as isoflavone) are mainly bound to beta-type estrogen receptor (ER- β) receptors³³, but the main receptor of estrogen is in the ER- α endometrium²⁶. Therefore, in cases where the dose Prescription is increased, bioavailability also increases and the binding of phytoestrogens to ER- α receptors increases.

In phytoestrogens application, it should be considered that postmenopausal women may not respond appropriately in increasing endometrial thickness^{35 - 36} and high concentrations of phytoestrogens can lead to infertility in women³⁷. It should be noted that the use of medicinal plants to increase the thickness of the endometrium may be depended on the dose, the endogenous estrogen status, the type of prescription and the form of the used chemical materials.

Furthermore, phytoestrogens sometimes have a by-phasic effect on the regulation of uterine receptors, and this should be considered in addition to the identification of synergistic drugs in the treatment process. Besides, the administration of phytoestrogens is not always beneficial and sometimes may lead to complications³².

It should not be forgotten that some plants may have a photographic result due to having estrogenic materials. In a study, it was shown that *Michelia champaca* L. has estrogenic compounds and administration of its hydroalcoholic extract to infertile mice causes weight gain, uterine weight gain, uterine thickening and vaginal cornification, all of which contribute to the prevention of successful implantation³³. On the other hand, the effective dose or exposure time of phytoestrogens has a decisive role in fertility. For example, Genistein, which is a phytoestrogen, does not show the same behavior at different doses.

Thus, at a specific dose, it reduced the thickness of the endometrium and, at a higher dose, it increased endometrial thickness³³.

It is shown that time is another important factor in the treatment by herbal phytoestrogens and in ART treatments, the factor of time should be considered based on the hormonal status of infertile women and the administration of herbal drugs or phytoestrogens to increase the chance of success. On the other hand, the side effects of herbs and their overdose should be paid attention. Although the side effects may not be noticeable to the patient or embryo during the length of the study, the point that was not evaluated in the studies was the implications of the use of these plants or their compounds on the embryo. As the results of studies indicated, taking some herbs during pregnancy can cause teratogenic complications³⁹⁻⁴⁰.

CONCLUSION: Medicinal plants and their derivatives, mainly due to phytoestrogens, influence on the thickness of the endometrium and can help maintain the fetus in the uterus and increase fertility. The phytoestrogens in plants are bound to ER- α receptors and mimics the function of estrogen. However, the effective dose, administration time, endogenous estrogen status and type of herbal prescription or derivatives are important considerations that should be considered in herbal treatments. But the effectiveness of herbs in increasing endometrial thickness and increasing fertility is still questioned, and this requires further research in this regard.

ACKNOWLEDGEMENT: This study was supported by Shahrekord University of medical sciences.

CONFLICT OF INTEREST: There was no conflict of interest.

REFERENCES:

- Shabaniyan S, Khalili S, Lorigooini Z, Malekpour A and Heidari-Soureshjani S: The effect of vaginal cream containing ginger in users of clotrimazole vaginal cream on vaginal candidiasis. *Journal of Advanced Pharmaceutical Technology and Research* 2017; 8: 80-84.
- Yavangi M: Use of Iranian Medicinal Plants Effective on Male Fertility Indices. *Journal of Global Pharma Technology* 2017; 8: 36-43.
- Yavangi M: A Systematic Review of Iranian Medicinal Plants Effective on Female Infertility. *Journal of Global Pharma Technology* 2017; 8: 44-49.
- Nikfarjam M, Bahmani M and Heidari-Soureshjani S: Phytotherapy for anxiety in Iran: A review of the most important Anti-anxiety medicinal plants. *Journal of Chemical and Pharmaceutical Sciences* 2016; 9(3): 1235-1241.
- Nikfarjam M, Bahmani M and Heidari-Soureshjani S: Phytotherapy for depression: A review of the most important medicinal plants of flora of Iran effective on depression. *Journal of Chemical and Pharmaceutical Sciences* 2016; 9(3): 1242-1247.
- Heidari-Soureshjani S, Asadi-Samani M, Yang Q and Saeedi-Boroujeni A: Phytotherapy of nephrotoxicity-induced by cancer drugs: an updated review. *Journal of Nephropathology* 2017; 6: 254-263.
- Asadi-Samani M, Raeisi R, Heidari-Soureshjani S and Asadi-Samani M: A review for discovering hepatoprotective herbal drugs with least side effects on kidney. *Journal of Nephro pharmacology* 2017; 6: 38-48.
- Solati K, Heidari-Soureshjani S, Luther T and Asadi-Samani M: Iranian medicinal plants effective on sexual disorders: A systematic review. *International journal of pharmaceutical sciences and research* 2017; 8: 2415-2420.
- Nikfarjam M, Heidari-Soureshjani S, Khoshdel A, Asmand P and Ganji F: Comparison of spiritual well-being and social health among the students attending group and individual religious rites. *World Family Medicine/Middle East journal of Family Medicine* 2017; 15: 160-165.
- Artimani T, Shabaniyan S, Heidari-Soureshjani S, Asadi-Samani M, Luther T and Branch S: A review of Iranian medicinal plants with teratogenic and abortion-inducing side effects. *International journal of pharmaceutical sciences and research* 2017; 8: 2372-2377.
- Ardestani-Samani N, Rabiei M, Ghasemi-Pirbalooti M, Bayati A and Heidari-Soureshjani S: Comparative study of self-concept, physical self concept, and time perspective between the students with multiple sclerosis and healthy students in Shahrekord. *World Family Medicine/Middle East Journal of Family Medicine* 2017; 15: 80-84.
- Ardestani-Samani N, Rabiei M, Ghasemi-Pirbalooti M, Bayati A and Heidari-Soureshjani S: Study and comparison of psychological disorders in normal students and students with multiple sclerosis in Shahrekord. *World Family Medicine/Middle East Journal of Family Medicine* 2017; 15: 75-79.
- Habibzadeh V, Nematollahi Mahani SN and Kamyab H: The correlation of factors affecting the endometrial thickness with pregnancy outcome in the IUI cycles. *Iranian Journal of Reproductive Medicine* 2011; 9: 41-6.
- Momeni M, Rahbar MH and Kovanci E: A meta-analysis of the relationship between endometrial thickness and outcome of in vitro fertilization cycles. *Journal of Human Reproductive Sciences* 2011; 4: 130-7.
- Mahajan N and Sharma S: The endometrium in assisted reproductive technology: How thin is thin? *Journal of Human Reproductive Sciences* 2016; 9: 3-8.
- Singh N, Bahadur A, Mittal S, Malhotra N and Bhatt A: Predictive value of endometrial thickness, pattern and sub-endometrial blood flows on the day of hCG by 2D doppler in *in-vitro* fertilization cycles: A prospective clinical study from a tertiary care unit. *Journal of Human Reproductive Sciences* 2011; 4: 29-33.
- Wolff EF, Vahidi N, Alford C, Richter K and Widra E: Influences on endometrial development during intrauterine insemination: clinical experience of 2,929 patients with unexplained infertility. *Fertility and sterility* 2013; 100: 194-9.e1.

18. Satirapod C, Wingprawat S, Jultanas R, Rattanasiri S, Jirawatnotai S and Choktanasiri W: Effect of estradiol valerate on endometrium thickness during clomiphene citrate-stimulated ovulation. *The journal of obstetrics and gynaecology research* 2014; 40: 96-101.
19. Quaas AM, Kono N, Mack WJ, Hodis HN, Felix JC, Paulson RJ, *et al.*: The effect of isoflavone soy protein supplementation on endometrial thickness, hyperplasia and endometrial cancer risk in postmenopausal women: A randomized controlled trial. *Menopause (New York, NY)* 2013; 20: 840-4.
20. Hebbar S, Chaya V, Rai L and Ramachandran A: Factors Influencing Endometrial Thickness in Postmenopausal Women. *Annals of Medical and Health Sciences Research* 2014; 4: 608-14.
21. Pedram A, Razandi M, Lewis M, Hammes S and Levin ER: Membrane-localized Estrogen Receptor Alpha is required for Normal Organ Development and Function. *Developmental cell* 2014; 29: 482-90.
22. Backes FJ, Walker CJ, Goodfellow PJ, Hade EM, Agarwal G, Mutch D, *et al.*: Estrogen receptor-alpha as a predictive biomarker in endometrioid endometrial cancer. *Gynecol Oncol* 2016; 141: 312-7.
23. Yavangi M: Use of Iranian Medicinal Plants Effective on Male Fertility Indices. *Journal of Global Pharma Technology* 2017; 8: 36-43.
24. Yavangi M: A Systematic Review of Iranian Medicinal Plants Effective on Female Infertility. *Journal of Global Pharma Technology* 2017; 8: 44-9.
25. Shabaniyan S, Kalbasi S, Shabaniyan G, Khoram B and Ganji F: The Effect of Metoclopramide Addition to Lidocaine on Pain of Patients with Grades II and III Post-Episiotomy Repair. *Journal of Clinical and Diagnostic Research* 2017; 11: QC11-QC4.
26. Shabaniyan S, Farahbod F, Rafieian M, Ganji F and Adib A: The effects of Vitamin C on sperm quality parameters in laboratory rats following long-term exposure to cyclophosphamide. *Journal of Advanced Pharmaceutical Technology and Research* 2017; 8: 73-9.
27. Shabaniyan S, Kazemi-Vardanjani A and Bahmani M: Trichomoniasis phytotherapy: An overview of the most important medicinal plants affecting *Trichomonas vaginalis*. *Journal of Chemical and Pharmaceutical Sciences* 2016; 9: 1255-62.
28. Shabaniyan S, Bahmani M and Asadi-Samani M: The medicinal plants effective on female hormones: A review of the native medicinal plants of Iran effective on estrogen, progesterone, and prolactin. *Journal of Chemical and Pharmaceutical Sciences* 2016; 9: 1270-6.
29. Shahin AY and Mohammed SA: Adding the phytoestrogen *Cimicifugae racemosae* to clomiphene induction cycles with timed intercourse in polycystic ovary syndrome improves cycle outcomes and pregnancy rates - A randomized trial. *Gynecol Endocrinol* 2014; 30: 505-10.
30. Monsees TK and Opuwari CS: Effect of rooibos (*Aspalathus linearis*) on the female rat reproductive tract and liver and kidney functions *in vivo*. *South African Journal of Botany* 2017; 110: 208-15.
31. Kamel HH: Role of phyto-oestrogens in ovulation induction in women with polycystic ovarian syndrome. *Eur J Obstet Gynecol Reprod Biol* 2013; 168: 60-3.
32. Le AW, Wang ZH, Dai XY, Xiao TH, Zhuo R, Zhang BZ, *et al.*: An experimental study on the use of icariin for improving thickness of thin endometrium. *Genetics and Molecular Research* 2017; 16.
33. Gao X, Chang X, Du H, Zhang M, Zhang J and Zhu A: Effect of soothing liver therapy on oocyte quality and growth differentiation factor-9 in patients undergoing *in vitro* fertilization and embryo transfer. *Journal of Traditional Chinese Medicine* 2013; 33: 597-602.
34. Zin SRM, Omar SZ, Khan NLA, Musameh NI, Das S and Kassim NM: Effects of the phytoestrogen genistein on the development of the reproductive system of Sprague Dawley rats. *Clinics* 2013; 68: 253-62.
35. Xue L, Wang Y, Jiang Y, Han T, Nie Y, Zhao L, *et al.*: Comparative effects of er-xian decoction, epimedium herbs, and icariin with estrogen on bone and reproductive tissue in ovariectomized rats. *Evidence-based complementary and alternative medicine* 2012; 24:1416.
36. Quaas AM, Kono N, Mack WJ, Hodis HN, Felix JC, Paulson RJ, *et al.*: Effect of isoflavone soy protein supplementation on endometrial thickness, hyperplasia, and endometrial cancer risk in postmenopausal women: A randomized controlled trial. *Menopause* 2013; 20: 840-4.
37. Seppen J: A diet containing the soy phytoestrogen genistein causes infertility in female rats partially deficient in UDP glucuronyl transferase. *Toxicol Appl Pharmacol* 2012; 264: 335-42.
38. Taprial S, Kashyap D, Mehta V, Kumar S and Kumar D: Antifertility effect of hydroalcoholic leaves extract of *Michelia champaca* L.: An ethnomedicine used by Bhatra women in Chhattisgarh state of India. *Journal Ethnopharmacol* 2013; 147: 671-5.
39. de Araujo CR, Santiago FG, Peixoto MI, de Oliveira JO and Coutinho Mde S: Use of Medicinal Plants with Teratogenic and Abortive Effects by Pregnant Women in a City in Northeastern Brazil. *Revista Brasileira de Ginecologia e Obstetrícia / RBGO Gynecology and Obstetrics* 2016; 38: 127-31.
40. John LJ and Shantakumari N: Herbal Medicines Use during Pregnancy: A Review from the Middle East. *Oman Medical Journal* 2015; 30: 229-36.

How to cite this article:

Farahbod F and Heidari S: A systematic review of medicinal plants and plant derivatives affecting increase in endometrial thickness. *Int J Pharm Sci & Res* 2018; 9(1): 53-57. doi: 10.13040/IJPSR.0975-8232.9(1).53-57.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)