



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

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### Keywords:

Infertility,  
Endometrial thickness,  
Medicinal plants, herbal therapy

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**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- $\alpha$  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 diseases<sup>1-8</sup>. 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 diseases<sup>9-12</sup>.

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 pregnancy<sup>13</sup>. 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 treatment<sup>14-16</sup>.

In some cases infertility therapists do not care about infertility treatments, thus therapeutic approaches should be adopted for it<sup>17</sup>. As the low thickness of the endometrium causes problems in endometrial glandular growth and angiogenesis,

<p><b>QUICK RESPONSE CODE</b></p> 	<p><b>DOI:</b> 10.13040/IJPSR.0975-8232.9(1).53-57</p> <hr/> <p>Article can be accessed online on: <a href="http://www.ijpsr.com">www.ijpsr.com</a></p>
<p>DOI link: <a href="http://dx.doi.org/10.13040/IJPSR.0975-8232.9(1).53-57">http://dx.doi.org/10.13040/IJPSR.0975-8232.9(1).53-57</a></p>	

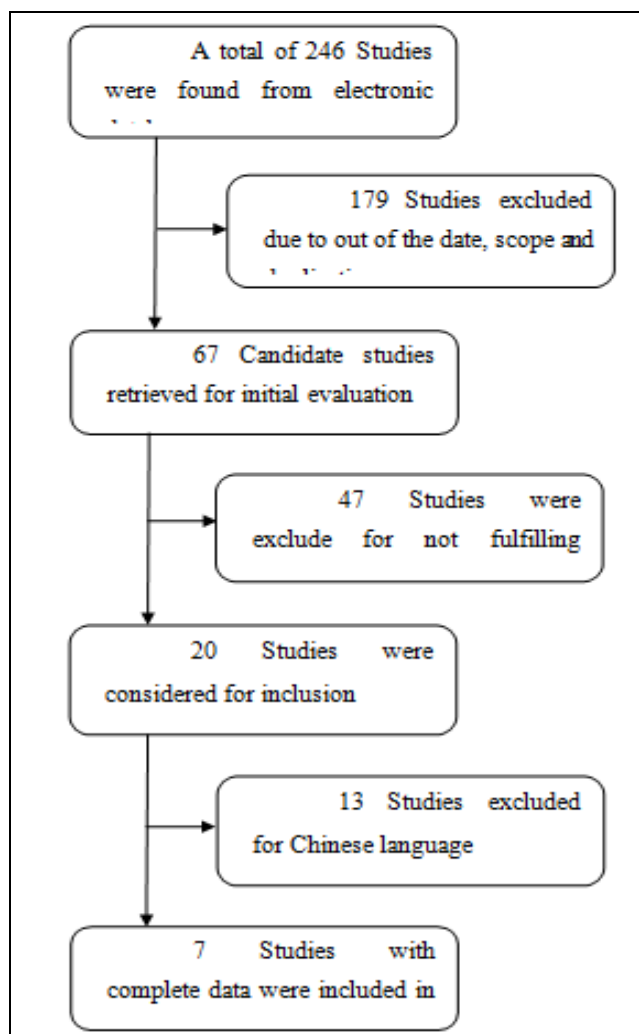
and by doing these changes, the vascular endothelial growth factor (VEGF) is reduced. In other words, the implantation and vascularization are weaker than the effects of low endometrial thickness, which causes early abortion<sup>15</sup>.

Estrogen therapy is used as one of the effective factors in the treatment of low endometrial thickness without disorder in folliculogenesis and ovulation<sup>18</sup>. Estrogen is received by estrogen receptor alpha (ER- $\alpha$ ), and estrogen prevents endometrial tissue atrophy and helps to grow and increase its thickness<sup>19-22</sup>.

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 infertility<sup>17-27</sup>, 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 PCOS<sup>28</sup>.

***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 mice<sup>29</sup>.

**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 women<sup>30</sup>.

**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 VIII<sup>31</sup>.

**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 cells<sup>32</sup>.

**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 group<sup>33</sup>. 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- $\alpha$ )<sup>34</sup>.

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 observed<sup>34</sup>. 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 normal<sup>29</sup>.

Phytoestrogens (such as isoflavone) are mainly bound to beta-type estrogen receptor (ER- $\beta$ ) receptors<sup>33</sup>, but the main receptor of estrogen is in the ER- $\alpha$  endometrium<sup>26</sup>. Therefore, in cases where the dose Prescription is increased, bioavailability also increases and the binding of phytoestrogens to ER- $\alpha$  receptors increases.

In phytoestrogens application, it should be considered that postmenopausal women may not respond appropriately in increasing endometrial thickness<sup>35 - 36</sup> and high concentrations of phytoestrogens can lead to infertility in women<sup>37</sup>. 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 biphasic 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 complications<sup>32</sup>.

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 implantation<sup>33</sup>. 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 thickness<sup>33</sup>.

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 complications<sup>39-40</sup>.

**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- $\alpha$  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.

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**How to cite this article:**

Farahbod F and Soureshjani SH: 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.

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