Protective role of ginseng in endometriosis during covid-19

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The coronavirus disease 2019 (COVID) pandemic began in December 2019. Many countries have implemented restrictions such as mandatory mask wearing and social distancing. These measures have caused diverse and complex health problems, particularly in women’s health, anxiety, and depression. This review examines an alternative approach to the treatment of endometriosis during the COVID pandemic. The efficacy of ginseng with anti-inflammatory activity and ability to relieve or prevent symptoms of endometriosis is discussed and reviewed.

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1. Introduction

Around the end of 2019, a series of cases of pneumonia of unknown cause occurred in Wuhan, Hubei, China [1]. The clinical manifestations were like those of viral pneumonia. On January 7, the China Centers for Disease Control and Prevention found a novel coronavirus in these patients and reported that it had caused the cluster of pneumonia cases. The World Health Organization estimated that 527,842,668 patients caught COVID and 6,300,942 died between December 30, 2019, and January 3, 2022 [2]. COVID causes symptoms such as chest and sore throat, muscle pain, fever, cough, and respiratory insufficiency. It affects the heart, liver, kidney, and nervous system [3,4]. COVID is also responsible for multi-organ syndrome [5,6]. Neurological symptoms including depression, musculoskeletal, and digestive such as diarrhea are frequently observed in patients with post-COVID syndrome. Causes of post-COVID syndrome are under study. Hypotheses including autoimmune problem, persisting chronic inflammation, and hormonal imbalance as a consequence of a change in the hypothalamic-pituitary-adrenal axis have been proposed [7]. To prevent the spread of the virus by contact, a stringent approach has been taken. Measures include implementation of social distancing, mandatory use of face masks, events cancellation (e.g., meetings, exhibitions, and sports competitions), strict travel restrictions, and closure of most nonessential workplaces. Most countries have adopted these precautions to limit the spread of COVID. However, these measures themselves have caused a health crisis, worsening mental health and increasing numbers of suicides [8,9]. Endometriosis is one of the most common benign gynecological conditions in premenopausal women. An estimated 10–15% of women of reproductive age have pelvic endometriosis [10]. Endometriosis is a pelvic inflammatory disease triggered by inflammatory reactions caused by evasion of the local immune system [11]. It can lead to abrupt abdominal pelvic pain and reproductive problems such as infertility [12]. Local pre-inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β can activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and hypoxia-inducible factor 1-alpha (HIF-1α) signaling pathways, leading to cyclooxygenase-2 (COX-2) induction and angiogenesis [11]. A positive feed-forward loop is created by COX-2 to enhance inflammatory activity and ability to relieve or prevent inflammatory reactions caused by COX-2 induction and angiogenesis [11]. These data suggest that suppression of COX-2 is a promising therapeutic strategy for endometriosis [14]. The COVID pandemic has had many mental and physical adverse effects on women’s health, anxiety, and depression [15,16]. An internet-based survey for assessing the impact of COVID was carried out on the care of people with endometriosis worldwide, to determine their priorities in relation to their clinical care during and after COVID, and whether they believed that endometriosis made them more vulnerable to COVID. Issues reported by 80.7% out of 6729 eligible respondents with endometriosis included difficulties obtaining medication (20.3%), and sports competitions), strict travel restrictions, and closure of most nonessential workplaces. Most countries have adopted these precautions to limit the spread of COVID. However, these measures themselves have caused a health crisis, worsening mental health and increasing numbers of suicides [8,9]. Endometriosis is one of the most common benign gynecological conditions in premenopausal women. An estimated 10–15% of women of reproductive age have pelvic endometriosis [10]. 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attenuate TNF-β by inhibiting activation of NF-κB, vascular cell adhesion molecule-1, MCP-1, IL-8, and IL-6 functions, and diseases such as breast cancer [19]. Genistein can been assessed clinically in endometrial carcinoma, endothelial cells [22]. Curcumin can maintain immune system homeostasis and enhance resistance against endometriosis associated symptoms by regulating angiogenesis, inflammation, and anti-inflammatory suppression, increasing apoptosis, immune system regulation, and anti-inflammation, [24–30]. The following section focused on KRG of its effectiveness for endometriosis.

### 2. Endometriosis and herb

Curcumin, genistein, ginsenoside, resveratrol, and pueraerin have been assessed clinically in endometrial carcinoma, endothelial functions, and diseases such as breast cancer [19]. Genistein can inhibit the maintenance of endometriosis controlled by vascular endothelial growth factor (VEGF) and suppress neo-angiogenesis by inhibiting HIF-1α and mitogenic activity [20]. Curcumin can attenuate TNF-α-stimulated expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, MCP-1, IL-8, and IL-6 by inhibiting activation of NF-κB, a key regulator of inflammation and inflammation gene activation, in human endometriotic stromal cells [21]. Regulated on activation normal T cell-expressed and secreted (RANTES) is a potent chemotactic factor for monocytes and activated T lymphocyte [22]. It is produced by peritoneal macrophages and endometriotic stromal cells. Its concentrations and levels are elevated in endometriotic patients, paralleling with disease severity. It is increased by the synthesis of cytokines (such as IL-1β) by activated macrophages and of NF-κB by endometriotic stromal cells [23]. Resveratrol can significantly reduce the expression of RANTES in ectopic endometrial stromal cells [23]. Several Chinese medicine formula containing various Chinese herbs were reviewed which can relieve various symptoms such as dysmenorrhea relief, reduction of CA-125, normalization of prolactin serum levels, treatment of uterine fibroids and even infertility [19].

### 3. Ginseng and endometriosis

Korea red ginseng (KRG) has immunomodulatory [28,31,32], anti-inflammatory [32–36], and anti-proliferative effects [37,38]. It can maintain immune system homeostasis and enhance resistance to microbial attack by regulating the immune system. The production of TNF-α, IL-18, IL-12, IL-6, IL-1β, and interferon-gamma (IFN-γ) is controlled by KRG [34,38–42]. KRG attenuates not only the production of pro-inflammatory cytokines, but also the production of chemokines such as MCP-1 and MIP-2β thereby reducing leukocyte infiltration and the inflammatory response [43].

### Table 1

| Bioactive herbal compound | Source | Model | Action/mechanism | Reference |
|--------------------------|--------|-------|------------------|-----------|
| Curcumin | Turmeric. | Ishikawa epithelial endometrial cells | Angiogenesis suppression and inflammation, anti-inflammation, antioxidant. | [66] |
| Resveratrol | Mulberry, peanuts, grapes, raspberry, cranberry, etc. | Ishikawa epithelial endometrial cells | Lowered IGF-1 and HGF levels | [65] |
| Quercetin | Onions, curry plagues, apple peels, lettuce, peppers. | Endometriotic stromal cells | Anti-angiogenesis, anti-inflammatory. | [68] |
| Apigenin | Apple, beans, broccoli, celery, cherry, grape, onion, parsley, tomato, tea, wine, etc. | Endometriotic stromal cells | Anti-angiogenesis, anti-inflammatory. | [69] |
| Rosmarinic acid and carnosic acid | Lamiaceae hub | Endometriotic stromal cells | Anti-angiogenesis, anti-inflammatory. | [69] |
| Wogonin | Scutellaria baicalensis | Immortalized endometrial cell (T-HESC, ATCC CRL-4003) | Anti-angiogenesis, anti-inflammatory. | [70] |
| Delta-9-tetrahydrocannabinol | Hemp | Ishikawa epithelial endometrial cells | Anti-angiogenesis, anti-inflammatory. | [71] |

### Table 2

| Source | Model | Action | Target | Reference |
|--------|-------|--------|--------|-----------|
| Rg3 | Female Sprague-Dawley (SD) | Angiogenesis suppression and increasing apoptosis | VEGFR-2-mediated PI3K/Akt/mTOR | [27] |
| Rg3 | Endometriotic stromal and Ishikawa cells | Inhibition of endometriosis-related fibrotic and invasion potential | miR-27b-3p | [26] |
| Rg3 | Female C57Bl6 mice | Reduction lesion size, fibrotic and invasion potential | MMP9, MMP2, fibronectin, CTGF, Col-1, TGF-β | [26] |
| Rg3 | Endometriotic stromal cells | Suppression of cell proliferation, angiogenesis, and inflammation. | NF-κB p65 subunit, VEGF | [25] |
| PPD | Endometriotic stromal cells | Activation of the cytotoxicity of NK, autophagy induction, growth of lesions suppression, enhancing immune surveillance | ERα, PRα | [24] |
| PPD | Female BALB/c mice | Reduction of lesion size, inflammation, and the risk of abortion | IL-12, IFN-γ, CD16, NKp30, K67, VEGF, TGF-β | [29] |
| Red ginseng | Female C57Bl6 mice | Reduction of lesion size, immune system regulation | miRNA | [30] |
| Red ginseng | DEHP-treated Ishikawa cells | Anti-inflammation | MMP-9, COX-2 | [31] |
inflammatory effects of KRG are associated with cytokine regulation and phagocytosis in innate immunity as well as the activation of B and T lymphocytes [44–46]. Ginsenosides such as ginsenoside-Rh2 (Rh2) and ginsenoside-Rg3 (Rg3) and their metabolites propanaxatriol (PPT) and propanaxadiol (PPD) have antioxidant, anti-tumor, anti-inflammatory and immunomodulatory activities [47–51]. For instance, Rg3 can significantly reduce the activity of NF-κB, elevate caspase-3 expression, and inhibit VEGF expression [52–56]. These effects of KRG may be beneficial to symptoms of post-COVID as well autoimmune problems, persistent chronic inflammation, and hormonal imbalance as a consequence of changes in the hypothalamic-pituitary-adrenal axis [75,77].

We have reported that KRG can attenuate phthalate-induced endometriosis in a mouse model as indicated by a reduction in the expression of CD10, a sensitive marker of endometrial stromal cells [13]. COX-2 is overexpressed in endometriosis. COX-2 can induce or promote proliferation and inflammation [14]. KRG can decrease COX-2, NF-κB, and EKIK1/2 levels in Ishikawa cells. It can inhibit COX-2 through diverse mechanisms, including the suppression of NF-κB [13]. Therefore, KRG can alleviate or prevent endometriotic symptoms. PPT and Rh2 can inhibit the viability and growth of ectopic endometrial stromal cells [24]. In endometriosis, PPD can reduce ectopic foci, promote endometrial receptivity and decidualization, suppress the inflammatory response of peritoneal macrophages, and increase the proportion, tolerance, and pro-angiogenic phenotypes of natural killer cells. It can down-regulate estrogen receptor α (ERα) and induce the expression of progesterone receptor in ectopic and normal endometrial stromal cells. ERα suppression mediated by PPD can induce autophagy of ectopic endometrial stromal cells, leading to increased NK cell cytotoxicity. These phenomena can enhance the immune surveillance of ectopic lesions thus inhibiting the development of endometriosis [24,29]. In a rat model, Rg3 can inhibit the development of endometriotic lesions induced by endometrial tissue allotransplantation by inhibiting angiogenesis [27]. Other studies have shown that Rg3 can inhibit the proliferation of ectopic endometriotic cells and significantly diminish the level of NF-κB p65 subunit as well as TNF-α induced nuclear translocation of NF-κB p65 subunit in ectopic endometriotic cells [25]. In addition, it can suppress endometriosis by regulating apoptosis and angiogenesis via NF-κB signaling in human ectopic endometrial stromal cells, suggesting that it can inhibit the growth of ectopic endometrium by blocking VEGF receptor-2-mediated PI3K/Akt/mTOR signaling pathway, thus promoting the halting angiogenesis and apoptosis of ectopic endometrial cells [27]. In an endometriosis mouse model, red ginseng extract can significantly reduce the size of endometrial implant. Functional analyses have indicated that miRNAs with altered expression are involved in the immune system and multiple pathways, for example, PI3K/Akt/mTOR and Ras/Raf/MAPK pathways [30]. Through this regulation route, ginseng and its components can alleviate symptoms of endometriosis and inhibit the progression of endometriosis. Table 2 lists effects of KRG and its associated ginsenosides on endometriosis. The COVID-19 pandemic causes difficulties in endometriosis treatment and surgery [17]. Moreover, Covid-19 induced cytokine storms causing imbalances in inflammatory factors such as IL-6, IL-10 is believed to have an adverse effect on the health of endometriosis patients [58,59]. Therefore, it would be valuable to study the effectiveness of KRG on endometriosis under pandemic situation.

4. Conclusion

Medicinal plants can relieve fever and cough in patients with COVID [60]. KRG may modulate acquired and natural immunity during COVID infection, indicating its potential as a preventive and supportive therapy [37,60–62]. It can promote health and prevent diseases by having immunomodulatory [63,64]. This review summarized a therapeutic potential of KRG as an adjunct for treating and preventing endometriosis [13,25–27,29,30]. Further focused research is needed to reveal the precise functional effect and the mechanism of action of KRG in endometriosis in conjunction with viral spread of pandemic situation.

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