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Review

Curcumin and endometriosis: Review on potential roles and molecular mechanisms

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ABSTRACT

Endometriosis, an estrogen-dependent inflammatory disease, is one of the most common chronic gynecological disorders affecting women in reproductive age. It is characterized by the presence of endometrial-like tissue outside the uterus. The exact pathophysiology of endometriosis is not still well-known, but the immune system and inflammation have been considered as pivotal factors in disease progression.

Turmeric, an important spice all around the world, is obtained from the rhizomes of Curcuma longa, a member of the Zingiberaceae family. It has been used in the prevention and treatment of many diseases since ancient times. Curcumin is the principal polyphenol isolated from turmeric. Several evidences have shown the anti-inflammatory, antioxidant, anti-tumor, anti-angiogenesis, and anti-metastatic activities of curcumin. In this review, relevant articles on the effect of curcumin on endometriosis and possible molecular mechanisms are discussed.

1. Introduction

Endometriosis is one of the most common gynecological disorders that characterized by the presence of glands and stroma outside the uterine cavity [1]. It affects 6–10% of women in reproductive age. The primary symptoms of the disease are infertility and pelvic pain. Other symptoms include dysmenorrhea, irregular uterine bleeding, dyspareunia, and dysuria [1–3]. Endometriotic lesions are often detected in the ovaries, fallopian tubes, the ligaments of the uterus, the cervical-vaginal area, abdominal, wall and umbilicus, urinary tract and also the rectum [4,5]. The American Society for Reproductive Medicine, has classified the disease from stage I (minimal endometriosis) to stage IV (severe endometriosis) according to the number, size, morphology, adhesion, and location of endometrial implants [6]. The clinical presentation of the disease is classified by the American Fertility Society as peritoneal endometriosis, endometriotic ovarian cysts and deeply infiltrating endometriosis (DIE). DIE, the most aggressive manifestation of endometriosis, is characterized by penetration more than 5 mm of endometrial implants into the affected tissues [7].

The pathogenesis of endometriosis has been much debated and various hypotheses have been postulated in disease pathogenesis. According to the Stem cell theory, undifferentiated stem cells like bone marrow-derived stem cells translocate to ectopic regions and differentiate to endometriotic lesions [8,9]. Metaplasia theory proposed that residual embryonic cells of the Wolffian or Mullerian ducts transform into endometrial tissue through hormonal and immunological factors [8]. Displacement of endometrial tissue outside the uterine cavity during organogenesis is another theory to describe endometriosis development [5]. Among the theories so far expressed, the Sampson's implantation theory is more accepted. According to this theory, through retrograde menstruation, some endometrial cells are transported into the peritoneal cavity. This phenomenon results in the implantation of the endometrial cells to the peritoneum and development of endometriotic lesions [10,11]. According to Sampson's theory, adhesion and proliferation of endometrial tissue, cellular invasion and neoangiogenesis are essential elements in the pathogenesis of endometriosis

Abbreviations: AP-1, activator protein-1; Bax, Bcl-2-associated X protein; Bcl-2, B cell lymphoma-2; CCl4, carbon tetrachloride; COX-2, cyclooxigenase-2; EGF, epidermal growth factor; ELAM-1, endothelial leukocyte adhesion molecule-1; FGF, fibroblast growth factor; GnRH, gonadotropin releasing hormone; GPx, glutathione peroxidase; HER-2, human epidermal growth factor receptor-2; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor-1α; HPV, human papilloma viruses; HUVEC, human umbilical vein endothelial cells; ICAM-1, intracellular adhesion molecule-1; IFN-γ, interferon-γ; IGF-1, insulin-like growth factor-1; Iκ-B, inhibitor of kappa B; IL-6, interleukin-6; IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein-1; MDA, malonaldehyde; MMP, matrix metalloproteinase; MT1MMP, membrane type 1 matrix metalloproteinase; MVD, microvessel density; NF-κB, nuclear factor-κB; Nrf2-Keap1, nuclear factor erythroid 2 related factor 2- Kelch ECH associating protein 1; PBMC, peripheral blood mononuclear cells; PDGF, platelet derived growth factor; PDGF-βR, platelet-derived growth factor-β receptor; ROS, reactive oxygen species; TAC, total antioxidant capacity; TGF-β, transforming growth factor-β; TIMP-2, tissue inhibitor of MMP-2; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor

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[12]. Thus, cytokines, growth and angiogenic factors, and adhesion molecules such as TNF-α, IL-6, IL-8, TGF-β, and VEGF have been implicated as inducers of attachment, proliferation, and neovascularization [11]. Definitely, the proliferation, invasiveness, and attachment to the extracellular matrix are greater in ectopic endometrial cells and these cells produce higher amounts of pro-inflammatory cytokines and growth factors compared with the eutopic cells [5].

Despite the relatively high prevalence and economic burden associated with the disease, its etiology remains elusive [13,14]. To date, several factors including genetic, epigenetic, anatomic, hormonal, immune, inflammatory, and lifestyle, have considered in disease etiology [2,9,14]. Some researchers reported that endometriosis is associated with the quality of life and psychological well-being. Depression and anxiety are the most common psychological disorders in endometriotic patients. Sleep disturbance, sadness, dissatisfaction, and loss of working ability are higher in women with endometriosis compared with healthy women [7,15].

The only certain method for diagnosis of endometriosis is histological analysis after laparoscopy [7,15]. Endometriosis is a chronic disease in which recurrence may be occurred. Hormone therapy, medication and surgery are used to alleviate the disease symptoms in patients. Pain-relievings, non-steroidal anti-inflammatory drugs, GnRH analogues, aromatase inhibitors, progestins, combined estrogen-progestin therapy, and selective progesterone receptor modulators are the most common recommendations [5,16,17]. In some severe conditions like DIE, surgery is the primary therapeutic [7]. The introduction of new agents can be effective in improving the condition of patients. Diet is a potentially modifiable risk factor for endometriosis and recently, dietary components and phytochemicals are considered as preventive and therapeutic agents in endometriosis [2,18].

2. Curcumin

2.1. Turmeric

Turmeric that is derived from the rhizome of *Curcuma longa* L., (Zingiberaceae) is used as a spice, flavors, and color, all around the world. It is native to Asia and it was used in Ayurveda and Tibb-Unani in the treatment of numerous human diseases such as colic, toothaches, chest pains, digestive problems, wounds, gynecological problems and menstrual difficulties since ancient times [19,20].

Turmeric has more than 300 biologically active components such as polyphenols, sesquiterpenes, diterpenes, triterpenoids, sterols, and alkaloids [21]. Curcuminoids, the phenolic compounds derived from turmeric, are responsible for its yellow color. The three main curcuminoids are curcumin, desmethoxycurcumin, and bis-desmethoxycurcumin [22].

2.2. Chemistry and health benefits of curcumin

Curcumin (diferuloylmethane), the most active polyphenol in turmeric, is a low molecular weight curcuminoid. It was first chemically characterized in 1910 and comprises 2–8% of most turmeric [23,24].

Curcumin is a strong anti-inflammatory agent. According to literature, clinical trials have inconsistent results about the effects of curcumin in various disorders [25–28]; but up to now, the anti-oxidant, anti-inflammatory, hypoglycemic, wound healing, anti-microbial, anti-tumor, anti-angiogenic, anti-mutagenic, anti-metastatic, and hormonal regulatory properties of curcumin were reported by numerous in-vitro and animal studies [19,20,29–31]. Curcumin can inhibit chronic inflammation induced diseases such as cancer through various intrecellular and extracellular molecular pathways. Several studies have documented the role of curcumin in the prevention and treatment of various cancers, including gastrointestinal, respiratory, lymphatic, skin and reproductive system [32].

2.3. Pharmacokinetic of curcumin

The absorption and metabolization of curcumin affect its biological activity. Pharmacokinetic studies have confirmed that intestine and liver are major organs for curcumin metabolism [29]. Dietary curcumin is partially absorbed in the intestine [33]. A considerable portion of the ingested curcumin is not absorbed, reaches the cecum and colon and excretes [34]. The main part of ingested curcumin is conjugated with glucoronate and sulfate in the intestine and only negligible unconjugated curcumin is shown in plasma and other organs. After oral curcumin administration, serum concentrations peak at 1–2 h and are undetectable by 12 h. The major biliary metabolites in rats are glucuronides of tetrahydrocurcumin and hexahydrocurcumin [29,35,36].

The bioavailability of curcumin is modest because of its poor absorption, low water solubility, rapid metabolism and systemic elimination. Therefore, numerous strategies are made to enhance its bioavailability include using the curcumin metabolic pathway blockers, nanoparticles, liposomes, phospholipid complexes, and structural analogues [29,37].

2.4. Safety of curcumin

Curcumin is classified as ‘Generally Recognized As Safe’ by the United States Food and Drug Administration [38]. The only reported side effect of curcumin in one study was diarrhea [39].

The safety and tolerability of curcumin at high doses in human were evaluated by several clinical trials. Anecdotal reports suggest that dietary intake of turmeric up to 1.5 g per day, equal to about 150 mg per day of curcumin, is well-tolerated in human [40]. Some other studies claimed that oral doses of curcumin up to 8 and 12 g per day were safe and well tolerated in patients with pancreatic cancer and healthy volunteers, respectively [41–43].

3. Molecular mechanisms of curcumin related to endometriosis

So far, there are limited in-vitro and in-vivo studies investigated the effects of curcumin on endometriosis and its complications. In this review, some recent studies on the effect of curcumin on endometriosis and possible molecular mechanisms are discussed.

3.1. Cell proliferation and apoptosis

Based on literatures, the endometrial cells from women with endometriosis are different from women without the disease. In endometriosis, proliferation and the ability of endometrial cells to implant in ectopic locations and survive, increases. Proliferation markers indicated an increase in stromal and epithelial proliferation of eutopic endometrium in the proliferative phase in endometriosis patients. Also, the apoptosis of the eutopic and ectopic endometriotic cells is greatly lower in women with endometriosis compared with free-endometriosis women due to either intrinsic or brought about by environmental factors. A reduced sensitivity of endometriotic cells to apoptosis could promote the dissemination and implantation of these cells to ectopic sites. This reduced apoptosis is associated with the increased expression of anti-apoptotic factors (e.g., Bcl-2) and decreased expression of pro-apoptotic factors (e.g., Bax) [44–49].

So far, some studies have investigated the effects of curcumin on cell proliferation and apoptosis in endometriosis. In a study conducted by Zhang et al. to assess the effect of curcumin on endometriosis, eutopic endometriotic stromal and epithelial cells and normal endometrial stromal and epithelial cells were isolated from eight premenopausal endometriosis patients (aged 24–45 years). The cells were cultured in medium containing curcumin at concentration of 10, 30 or 50 μM at various time points ranging from 24, 48, 72, and 96 h. Results showed that curcumin decreased the growth and number of endometriotic stromal cells in a dose-dependent manner [50].