Biomedicine & Pharmacotherapy 91 (2017) 220–228

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

Resveratrol and endometriosis: In vitro and animal studies and underlying mechanisms (Review)

Roya Kolahdouz Mohammadi, Tahereh Arablou*

Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Hemmat Highway, 1449614535, Tehran, Iran

ARTICLE INFO

Article history:
Received 26 February 2017
Received in revised form 16 April 2017
Accepted 17 April 2017

Keywords:
Resveratrol
Endometriosis
In-vitro studies
Animal studies
Review

ABSTRACT

Endometriosis is characterized by the existence of endometrial tissue and stroma exterior to the uterus. Despite the high prevalence, the etiology of endometriosis remains elusive. The search for the most promising compounds for treatment of endometriosis has led to the identification of resveratrol. Resveratrol, a plant-derived polyphenolic phytoalexin, demonstrates broad-spectrum health beneficial effects, including anti-proliferative, anti-inflammatory, antineoplastic and antioxidant. Because of these properties and its wide distribution in plants, resveratrol is proposed as a great potential to treat endometriosis.

In animal models of endometriosis, resveratrol supplementation has displayed beneficial results as it decreased the number and volume of endometrial implants, suppressed proliferation, vascularization, inflammation, cell survival and increased apoptosis. On the other hand, resveratrol treatment in-vitro studies, reduced invasiveness of endometriotic stromal cells (ESCs) and suppressed their inflammatory responses.

In this review, we will summarize the recent studies in in-vitro and animal studies on resveratrol and endometriosis.

Contents

Abbreviations: ROS, reactive oxygen species; DMBA, 7,12-dimethylbenz[a]anthracene; RNS, reactive nitrogen species; PF, peritoneal fluid; NF-kB, nuclear factor kappa B; NOS, nitric oxide synthase; COX, cyclooxygenase; DMSO, dimethyl sulfoxide; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; GST, glutathione S-transferase; NQO1, NAD(P)H: quinone oxidoreductase 1; HO-1, heme oxigenase-1; ESCs, endometriotic stromal cells; EECs, endometrial epithelial cells; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor; Bax, Bcl-2-associated X protein; CSCs, cancer stem cells; PGE2, prostaglandin E2; AMPK, adenosine monophosphate-activated protein kinase; TNF-α, tumor necrosis factor α; MCP-1, monocyte chemotactic protein 1; SIRT1, sirtuin-1; iNOS, inducible nitric oxide synthase; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; FGF, fibroblast growth factors; PDECGF, platelet-derived endothelial cell growth factor; TGF, transforming growth factor; HIF-1α, hypoxia inducible factors-alpha.

* Corresponding author.
E-mail address: t.arablou@yahoo.com (T. Arablou).

http://dx.doi.org/10.1016/j.biopha.2017.04.078
0753-3322/

1. Introduction

Endometriosis, characterized by the presence of endometrial tissue outside the uterine cavity, predominantly on the pelvic peritoneum and ovaries [1]. It affects 10–20% of all women of childbearing age and up to 50% of women with infertility [1,2]. Signs and symptoms vary in severity and include dysmenorrhea, chronic pelvic pain, pain during intercourse, and infertility. Up to now, several theories have been presented to explain the pathogenesis of endometriosis but, a unifying theory regarding the origin of endometriosis has remained mystifyingly indefinable [3]. However, according to Sampson's theory, retrograde menstruation followed by ectopic attachment of endometrial tissues, development of endometriotic lesions as a result of genetic and microenvironmental factors, degradation of the extracellular matrix, invasion of the peritoneum, and subsequent growth of endometrial stroma and glands are required to cause endometriosis [4]. This process induces inflammation and elevated levels of pro-inflammatory cytokines can recruit and activate granulocytes and macrophages that meaningfully elevate reactive oxygen species (ROS) [5,6]. However, whatever the pathophysiology of this disease is, endometriosis is regarded currently as a chronic, estrogen-dependent, and inflammatory disease [4].

In recent years, the relations between dietary factors and endometriosis have become a topic of interest mostly because of the observation that diet can influence endometriosis through effects on inflammation, estrogen activity, menstrual cyclicity, smooth muscle contractility, immune functions and prostaglandin metabolism [7]. The natural agent resveratrol, a phytoalexin, isolated from the roots and fruits of many plants. It has been shown that resveratrol as a powerful antioxidant, can prevent or slow the progression of a wide variety of age-associated illnesses, like cancer, for example, which shares some characteristics with endometriosis [8]. Resveratrol anti-tumor activities are mediated through several mechanisms and include inhibition of proliferation in association with cell cycle arrest, induction of apoptosis and differentiation, reduction of inflammation and angiogenesis, and inhibition of adhesion, invasion, and metastasis [9]. Considering that several of these pathways are relevant to the pathophysiology of endometriosis, this review is intended to interpret the existing in-vitro and animal studies on resveratrol and endometriosis, with a view to underlying mechanisms that provide a rationale for testing resveratrol clinically in human populations (Table 1 and Fig. 1).

2. Resveratrol

2.1. Chemistry

Resveratrol (trans-3,4′,5-trihydroxystilbene, $C_{14}H_{12}O_3$) is a phytoalexin, or plant antibiotic, produced by leaf tissues in response to fungal infection or exposure to ultraviolet light existing in *cis*- and *trans*-stereoisomeric forms. Exposure to heat and ultraviolet radiation can cause trans-resveratrol to isomerize to the *cis*-resveratrol [10,11]. Resveratrol has been detected in a wide variety of plant species, including Japanese knotweed, peanuts, different kinds of berries, legumes and grasses, but the primary sources of resveratrol are, grapes and red wines [12]. Several genera of fungi, including *Botryosphaeria, Penicillium, Cephalosporium, Aspergillus, Geotrichum, Mucor* and *Alternaria*, are also important sources of resveratrol [13].

2.2. Metabolism and bioavailability

Bioavailability and the metabolism of resveratrol have been widely studied in rodents and humans. Initial experiments in rats commenced by Bertelli et al. [14–16]. In their studies, peak plasma levels of resveratrol contained in wine were reached their maximum concentration about 30–60 min post oral intake and high concentration of resveratrol was detected in the liver and kidneys. Five years later, Soleas and coworkers in 2001 showed that at least 75% of resveratrol ingested in rats, was quickly absorbed via passive diffusion in the intestines [17] and based on isolated rat small intestine model, jejunum and, in a lower degree, ileum are involved in the absorption of resveratrol [18].

In humans, following resveratrol absorption via passive diffusion in the intestines, it is readily metabolized in the liver by phase-2 drug-metabolizing enzymes to form mainly glucuronide and sulphate derivatives and these conjugated forms of resveratrol predominantly circulate in serum [19]. In humans, following oral unmodified trans-resveratrol intake (25 mg/70 kg body weight), free polyphenol accounted for 1.7–1.9% of the peak serum concentrations of total resveratrol [20]. In another report the absorption of 25-mg oral dose of resveratrol was at least 70%, with peak plasma levels of resveratrol and metabolites of 2 μM (490 ng/mL) [19].

Renal excretion of resveratrol in animal models, started within hours after oral intake and increased in 12–24 h. In the kidney, resveratrol was present in its native form, whereas in urine, conjugated forms of resveratrol were greatest [21]. In human, the renal excretion time depended on the concentration of resveratrol present in plasma [21].

Toxicological data confirm that resveratrol at doses below 1 g and for short duration is well tolerated. Any adverse effects (mainly abdominal disorders), appear with doses of $\geq$0.5 g/day for long periods. However, these adverse events in some studies may not have been related to resveratrol as in some studies with a placebo group, patients in both groups exhibited similar disorders [22].

2.3. Health benefits of resveratrol

The first scientific interest in resveratrol came in 1992 which was related to the cardioprotective effect of resveratrol in wine, known as "French paradox" [11]. A few years later, Jang et al. were the first to demonstrate cancer chemopreventive activity of resveratrol in animal models of carcinogenesis. Resveratrol was shown to block all three stages (initiation, promotion, and progression) of carcinogenesis induced by 7,12-dimethylbenz[a] anthracene (DMBA) [23]. In the intervening years, resveratrol was found to act as an anti-inflammatory, anti-tumorigenic, and antioxidant agent [24–26]. It can also delay or attenuate many age-associated illnesses, including cancer, cardiovascular disease, diabetes, arthritis and neurodegenerative diseases [27,28].