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**ENDOMETRIOSIS AND OXIDATIVE-ANTIOXIDATIVE  
IMBALANCE STATUS. THE ROLE OF FLAVONOIDS,  
CURCUMIN AND N-ACETYLCYSTEINE**

***Abstract.** Endometriosis is a silent, unseen and painful female illness which is characterized by the presence of glands and stroma outside the uterine cavity. Approximately one in ten women in a reproductive age around the world suffer from endometriosis of whom nearly half is treated due to infertility. The pathogenesis and mechanisms that determines the occurrence of the disease are still unknown. Immunological factors have been observed in the initiation and development of*



*endometriosis. An imbalance between reactive oxygen species (molecules having an unpaired electron) and antioxidants leads to the upregulation of metalloproteinases, prostaglandins, cytokines and chemokines.*

**Keywords:** *endometriosis, inflammation, flavonoids, curcumin, oxidative stress*

## **1. Introduction**

Endometriosis is a common gynecological disorder with features of chronic inflammation. Pathological lesions mostly occur in the ovaries, fallopian tubes, the ligaments of the uterus, the urinary tract and the rectum. Intense pain, irregular uterine bleeding, dyspareunia are main symptoms which has a negative impact on mental and physical health [1]. Mental disturbances may express as a various form of anxiety and depression. An additional problem, which leads to a deterioration in the emotional condition of the patients is infertility [2]. It is estimated that evolution of the disease has a negative influence on the quality of life in approximately one third of the patients. The use of other nonconventional ways to alleviate the symptoms, such as healthy diet, herbal essences and others, is recommended. The attitude of patients towards the disease and its course, acceptance of life with a chronic disease seems important [3].

## **2. Purpose of this work**

This study aimed to discuss the potential role of flavonoids, N-acetylcysteine and curcumin in endometriosis by acting on inflammation and oxidative stress.

## **3. Materials and Methods**

A comprehensive literature review using electronic database Pubmed, was conducted. The review was limited to sources in English language. We considered articles published from April 2015 to March 2021. Keywords such as : “endometriosis”, “immunological markers”, “oxidative stress”, and various combinations of the above were used. Publications were selected if they related to studies concerning the potential role of polyphenols, flavonoids, N-acetylcysteine and curcumin in endometriosis. In addition, we manually reviewed the references for each article to find potentially missed studies. Besides, we identified 175 articles that were related to topics of interest. Finally, 23 studies were selected for analysis.

#### 4. Inflammation and oxidative stress

Inflammation and oxidative stress are potential factors involved in the pathophysiology of endometriosis [4]. Following Sampson's theory, uterine endometrium after menstruation may become overreactive and trapped outside the uterus by reaching the pelvis via transtubal retrograde flow. Endometrial cells may implant onto the peritoneum and abdominal organs, proliferate and cause chronic inflammation with formation of adhesions [5]. Within the peritoneum of women with endometriotic changes, macrophages are highly activated with concomitant increased levels of proinflammatory mediators such as Interleukin-10 (IL-10, IL-6, IL-8, COX2 (cyclooxygenase-2), VEGF (vascular endothelial growth factor) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), which may alter the pathogenesis of this disease [6]. The above process is likely due to cellular failure and humoral immune response, the role of which is to inhibit implantation of endometrial tissue [7].

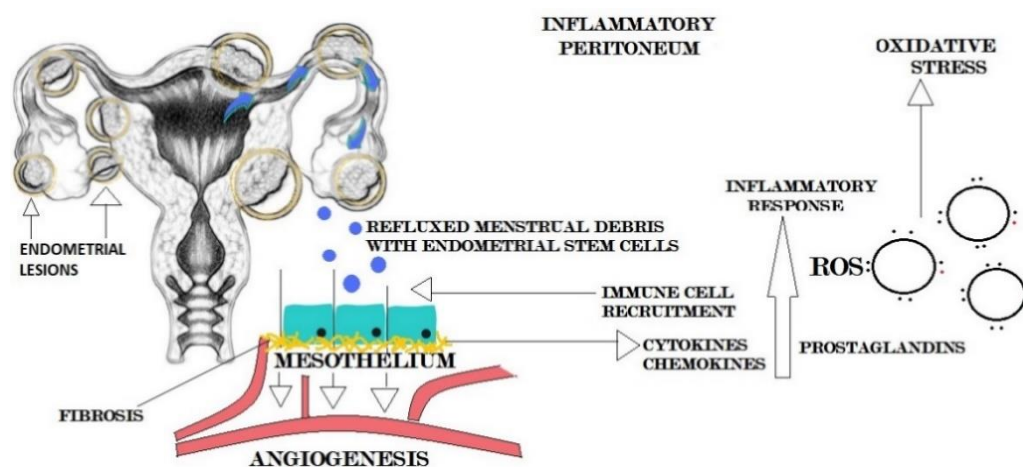


Fig. 1. Sampson's theory of retrograde menstruation

An oxidative stress is described as an imbalance between oxidative and inoxidative processes in an organism [8]. Macrophages and apoptotic endometrial tissue transplanting into the peritoneal cavity are thought to be inducers of oxidative stress in women suffering from endometriosis [9]. Erythrocytes located in peritoneum are present in approximately 90% of menstruating women [10]. Red blood cells may release heme and iron to the peritoneal environment during phagocytosis in macrophages [11]. These two components play essential role in

ROS (Reactive Oxygen Species) formation. As a consequence of oxidative stress peritoneal mesothelium is destructed and apoptosis is promoted. Chronic inflammation and repair are susceptible to fibrosis. Fibrotic scarring is formulated due to excessive accumulation of extracellular matrix components and is causing chronic pelvic pain and infertility in women [12].

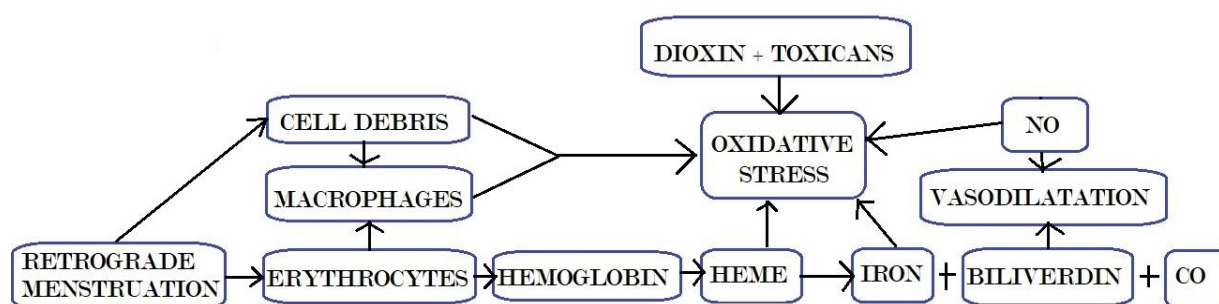


Fig. 2. **The genesis of Oxidative stress in the peritoneal cavity of women with endometriosis**

### 5. Flavonoids, curcumin and N-acetylcysteine in endometriosis

A proper diet is an important issue in endometriosis. It should focus on reducing inflammation, improving the hormonal balance, and ensuring a stable blood glucose level. Antioxidants are compounds which inhibit oxidation - reaction that can produce free radicals and chain reactions that may damage the cells of organisms. They occur in turmeric, yellow pepper, mustard, lemon, nuts, broccoli, cauliflower, carrots, pumpkin and others [13].

The first group of compounds are flavonoids. Resveratrol (trans-3,5,40-trihydroxystilbene) is a natural flavonoid synthesized by plants after exposure to ultraviolet radiation [14]. A high concentration of resveratrol may be found in grapes and mulberries. Flavonoids represent anti-inflammatory and antioxidant action by suppressing the expression of growth factors, decreasing cell proliferation, reducing the size of the ectopic implant, inducing an apoptosis, and oxidative stress [15]. Moreover, they inhibit the invasion, adhesion, and angiogenesis of endometriotic ectopic lesions. A long-term prospective study conducted in the US found that women who consumed one or more servings of citrus fruit per day had a 22% lower risk of endometriosis compared to those who consumed less than one servings per week [16].

Curcumin (bis- $\alpha$ ,  $\beta$ -unsaturated  $\beta$ -diketone) is a natural component which presents some therapeutically potential roles as anti-inflammatory guardian in the organism [17]. It can downregulate the expression of TNF- $\alpha$ , COX-2, IL-6 and TGF, TNF- $\alpha$ , IL-1, IL-6 and IL-8. Curcumin has been associated with a reduction of ROS serum, VEGF expression in ectopic endometrium, decreases the number of endometriosis stromal cells and the process of cell growth [18]. In addition, curcumin may inhibit cell proliferation and activates apoptosis in endometrial tumor cells [19].

Another representative that reduces the effects of oxidative stress and has anti-inflammatory properties is N-acetylcysteine [20]. N-acetylcysteine is a key substrate for the production of glutathione - an antioxidant compound responsible for detoxification processes [21]. It also affects the quality of oocytes and sperm, protecting DNA against free radicals [22]. In a study conducted by Iñaki et al 92.7% of the patients who assessed pain intensity  $> 4$  on the visual analogue scale (VAS), 3 months after treatment, 87.2% declared pain relief [23].

Summarizing, the limited number of studies focusing on the different interactions of antioxidants in endometriosis restricts its clear and immediate use in a therapeutic strategy. Future clinical trials are needed to better investigate and highlight the role of them.

## 6. Conclusions

- Investigating the mechanisms underlying oxidative stress associated with endometriosis may well prove useful for antioxidants in endometriosis treatment
- Dietary antioxidants can help reduce pain and improve the patient's quality of life
- The use of antioxidants is not able to reverse the disease, but it can definitely slow down its progression by acting on invasion, adhesion, apoptosis and angiogenesis in endometrial lesions

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