

The immunological impact of orthomolecular medicine using bioactive compounds as key factors in endometriosis

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ABSTRACT

Endometriosis, an inflammatory, non-lethal, non-malignant disease, still has unjustified etiology. Among many, the theory dealing with this review claims that a suppressed or incompetent immune system that is totally unable to eradicate the non-hemopoietic mesenchymal endometriotic stem cell (MESC) escapes immune surveillance. As a result, there is migration and invasion of the aforementioned cell to ectopic tissues causing the disease.

This review focuses on bioactive compounds (i.e. vitamins and minerals) that may have the potential to boost the immune system rendering it capable to fight the MESC and, consequently, endometriosis. The use of vitamins and minerals, also called meganutrients, constitutes the known approach of orthomolecular medicine. However, when scrutinized these methods yield contradicting results but still merit attention. According to our review of the available scientific literature, compared to traditional medicine, which only regulates hormonal imbalances and alleviates pain, the orthomolecular approach is promising for successfully strengthening the immune system towards a curative outcome. However, the underlying mechanisms behind the action of the abovementioned natural bioactive ingredients appear numerous and often speculative, thereby remaining under examination.

Keywords: bioactive compounds, functional foods, endometriosis, orthomolecular medicine, mesenchymal endometriotic stem cell (MESC), immune system

INTRODUCTION

Endometriosis, from the ancient Greek endo= inside, metrawomb and iosisdisease due to a virus, is an inflammatory, non-lethal, and non-malignant disease affecting approximately 10% to 15% of all women of reproductive age [1] and 70% of women with chronic pelvic pain [2]. Endometriosis is defined as the presence of endometrial glands and stroma-like lesions outside of the uterus (ectopic endometrial implants) and associated with infertility and pelvic pain [1].

However, it is unknown whether infertility is due to the endometriotic state of women or whether other endometriosis-associated factors lead to infertility. Mechanisms proposed for the development of infertility in endometriotic women include a number of gynecologic reasons, already extensively described, in addition to other causes that include the use of chemicals, *Candida albicans* infection, or abnormalities [3-6]. Numerous reports present evidence that endometriosis is a genetic and pre-determined disease due to environmental, endocrinological, and immunological factors [5, 7-10]. However, the discovery and investigation of a non-hemopoietic mesenchymal stem cell (MESC) [11] has shown that MESC(s) can escape surveillance due a frail immune system not competent enough to intercept the immaturely senescent cell, allowing migration and invasion to ectopic tissues [12, 13]. Thus, certain constituents of foods, termed bioactive compounds, can provide beneficial health properties, such as anti-inflammatory and anti-fungal activity, antioxidant advantages and especially preventive action against disease [14]. These bioactive compounds have recently been defined by Dr. Martirosyan and Pisarski as “*primary and secondary metabolites of nutritive and non-nutritive natural components generating health benefits by preventing or managing chronic disease or its symptoms*” [14-15].

Furthermore, the Functional Food Center (<https://www.functionalfoodcenter.net/>) defines “functional foods” as “natural or processed foods that contain biologically-active compounds; which, in defined, effective non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, for the prevention, management, or treatment of chronic disease or its symptoms”. Nevertheless, while many studies have been published using bioactive compounds in defined and non-toxic amounts for various conditions, accessible information on endometriosis is particularly lacking. As a result, we attempted to succinctly present the action of beneficial endometriosis substances as a function of their dosage and effect. The use of meganutrients (vitamins and minerals), constituting the orthomolecular approach, has been shown to be successful when taken up by endometriotic subjects, as they are able to reduce pain, ease the disease *via* anti-inflammatory effects, and promote immunity, which may be a key factor in intercepting the MESC for preventing or correcting endometriosis.

THE CONCEPT OF ORTHOMOLECULAR MEDICINE AND ITS ACTION ON IMMUNE PARAMETERS RELATING TO ENDOMETRIOSIS

The term "orthomolecular" was first used by the two-time Nobel Laureate Linus Pauling in 1968 to characterize the treatment of disease with nutrients that are endogenous to the human body [16]. Orthomolecular, from the Greek ortho=correct, basically translates into "essential nutrient". Orthomolecular physicians treat disease by varying dosages of "correct molecules" that are required but not synthesized by the human body. Orthomolecular therapy can be preventive, protective, and/or corrective. Its practitioners prevent disease by helping patients against the dangerously polluted environment and nutrient-stripped refined foods. With the uptake of a megavitamin therapy and/or a load of meganutrients. For example, with calcium, vitamin C, and zinc patients may be protected from the harmful effects of lead, cadmium, and mercury. In fact, orthomolecular medicine began and still focuses on the correction of biochemical imbalances of disease and represents another form of alternative medicine aiming to maintain human health through nutritional supplementation [17]. The first megavitamin therapy report, as presented by Andrew Saul, was published back in 1935 when Claus Washington Jungeblut, MD, Professor of Bacteriology at Columbia University first published on vitamin C as prevention and treatment for polio [18]. In the same year, he also demonstrated that vitamin C could inactivate diphtheria toxin,

while the first report on endometriosis came out in 1940 by the Shute brothers revealing that vitamin E prevents endometriosis [18].

With birthing problems and infant mortality, the use of certain vitamins and supplements has well been documented [19]. Similarly, for endometriosis a number of vitamins, supplements and/or trace elements can be mentioned as their role on endometriosis. As a whole, they have been described (i.e. on endometriotic lesions, fertility, pain, hormonal and/or immune regulation). As discussed below, their beneficial action has been well documented in endometriosis and to immunological fortification of the organism. However, the enhancement of immunity observed has never been correlated to the induction of the proper conditions for the interception of the MESC at early stages, thereby to reverse the burden of the disease.

Accordingly, a thorough literature search has revealed the following results on endometriosis in relation to bioactive compounds:

- Omega -3 fatty acids in fish oil are known to improve immunity and have anti-inflammatory properties. They are especially important for endometriotic women as they increase the body's production of prostaglandin E1 (PGE1), helping to manage painful symptoms. Additionally, a 2013 study by Herington *et al.* using an experimental mouse model of endometriosis, demonstrated that in mice with a 10% supplemented fish oil diet, adhesion score and disease burden significantly reduced [20].
- Melatonin has anti-cancer and anti-inflammatory properties as studied by Güney *et al.*, in a mouse model of endometriosis [21]. The authors found that melatonin causes regression and atrophy of the endometriotic lesions in experimental mice.
- Medicinal cannabis: As endometriosis is a benign disease usually responding to natural substances with anti-cancer activity, one would expect *Cannabis sativa* extract (β -caryophyllene constituent of essential oil of *Cannabis sativa*) to have beneficial effects in endometriotic subjects. Indeed, suppression of the growth of endometriotic implants by 52.5% compared with controls when used at 10 mg/kg was demonstrated. Additionally, β -caryophyllene produced apoptosis in luminal epithelium of the cyst, as well as in endothelial cells of blood vessels [22]. An additional benefit, reduction in endometriosis-associated pain, was also reported [23].
- Diindolylmethane (DIM) supports the body in eliminating excess estrogen. DIM is derived from cruciferous vegetables like cauliflower and broccoli. It metabolizes estrogen into components easily assimilated and removed by the body and avoids the development of estrogen dominance [24, 25].
- Coenzyme Q10 (CoQ10) is a potential antioxidant and immune support. However, studied on endometriosis are lacking [26, 27].
- Resveratrol is a natural substance obtained from red wine that has anti-proliferative and anti-inflammatory properties [28]. The mechanisms/pathways of action of this naturally occurring compound have also shown that, in animal models of endometriosis, resveratrol supplementation displays beneficial results by decreasing the number and volume of endometrial implants, suppressing proliferation, vascularization,

inflammation, cell survival, and increasing apoptosis [29]. On the other hand, *in vitro* resveratrol treatment reduces invasiveness of endometriotic stromal cells (ESCs) and suppresses their inflammatory responses. [29]. A 2011 study by Bruner-Tran *et al.* has demonstrated that resveratrol inhibits development of experimental endometriosis *in vivo* and reduces endometrial stromal cell invasiveness *in vitro* [30]. In this study, nude mice were implanted with human endometriosis cells. The authors found that resveratrol decreased the number of endometrial implants by 60% and decreased total volume of implants by 80%, a quite impressive result for a naturally occurring supplement. Finally, in a 2017 randomized clinical trial, resveratrol at 40 mg/d given with monophasic contraceptive pill has not been found superior to placebo for treatment of pain in endometriosis [31].

- L-Carnitine, naturally produced in the human body and helping the body convert fat to energy, appears allegedly useful in endometriosis since it facilitates pregnancy by reducing embryo cell death and damage to oocytes or eggs in endometriosis-infertile women who are trying to get pregnant or undergoing *in vitro* fertilization [32]. However, when administered to young female mice, L-Carnitine has been shown to induce a pathological condition resembling stage IV human endometriosis accompanied by a marked degree of infertility. Accordingly, the use of this nutrient by young women may be potentially hazardous responsible for the onset of endometriosis at a later stage of their lives [33].
- Iron (found in clams, fortified cereals, liver, oysters, lean red meat and dried beans) prevents anemia, weakness and fatigue due to heavy bleeding. Women with endometriosis tend to have very heavy periods that can lead to an iron deficiency. This can cause anemia, which is characterized by extreme fatigue and weakness [34].
- Magnesium (abundant in bananas, barley, green beans, kelp, sunflower seeds, and raspberry leaves) is extremely important, as it is a mineral essential for activating chemical reactions, transporting glucose to the cells, and boosting the immune system. Magnesium is also a muscle relaxant decreasing cramping [35].
- Selenium (cabbage, celery, cucumbers, Brazil nuts, tuna, cod, and meats) has been historically given to cows by farmers to prevent endometriosis. Endometriosis hinders fertility, so farmers work hard to prevent a disease that results in fewer calves. Selenium boosts immune system; decreases inflammation associated with endometriosis when taken with vitamin E [36]. This mineral increases natural killer cells and mobilizes cancer-fighting cells. A supplement of selenium is advised for women with endometriosis. The best sources of selenium may be from plant foods. However, most soil is depleted in this trace element today, so plants are not able to take up this mineral [34].
- Zinc (in ginger root, oysters, lamb chops, and pecans) is critical for proper thymus gland and immune system function. Research has shown that daily intake of 30 mg of zinc reactivates the immune system with dramatic improvements after 6 months in those with zinc deficiency. This valuable mineral increases the production of white blood

cells that fight infection and helps them fight more aggressively. It also increases killer cells that fight against cancer and helps the release of antibodies. Zinc supplements have been shown to slow the growth of cancer. However, too much zinc in the form of supplements (more than 75 milligrams a day) can inhibit immune function [37].

- Vitamin A (found in apricots, broccoli, cantaloupe, carrots, eggs, milk, pumpkin, spinach, and squash) improves the immune system. Vitamin A is an antioxidant and helps lessen profuse menstrual bleeding [35].
- Vitamin B complex (in fortified cereals, beans, red meat, poultry, mollusks, and liver) helps break down proteins, carbohydrates, and fats in the body, helps keep estrogen levels naturally low, and helps produce good PGs. Women with endometriosis may produce high levels of PGE2, resulting in inflammation in tissues and painful cramping. One of the B vitamins, B6, has been shown to significantly reduce the intensity and duration of period pains, thereby helping many sufferers [38]. B vitamins are also crucial for the conversion of essential fatty acids into beneficial PGs having a relaxing effect on the womb muscles and anti-inflammatory properties [37].
- Vitamin C (berries, broccoli, cantaloupe, grapefruit, lemons, oranges, peppers, spinach, and strawberries) helps boost the immune system and fight off disease. Vitamin C is an antioxidant that helps control excessive bleeding and detoxifies pollutants [34].
- Vitamin D (found in fatty fish, such as tuna, mackerel, salmon, and fish oils; however, the main source of this vitamin is still sunlight exposure) is an important player in the regulation of inflammation, as its deficiency enhances inflammation and promotes immunosuppression through the expansion of T regulatory cells (Tregs) in a murine myometrium (the middle layer of uterus, in contact with the endometrium) model [39]. As established, tumor escapement from immune response is due to an immunosuppressive environment, thereby pointing to a potential relationship with the inability of the immune system to annihilate the MESC, since endometriosis accurately resembles a cancerous state without being lethal [40].
- Vitamin E (abundant in almonds, avocado, eggs, safflower oil, salmon, and sunflower oil) is known to ensure that animals have healthy uterine linings and used by farmers since the 1930's. Vitamin E improves the immune system and has been shown to relieve menstrual cramps in 70 percent of women within two menstrual cycles in endometriosis
- Beta carotene (in carrots, spinach, sweet potatoes, tomatoes, and cantaloupe) increases the number of infection-fighting cells, natural killer cells, and helper T-cells. Beta carotene is also a powerful antioxidant that mops up excess free radicals that accelerate ageing and converts to vitamin A in the body [41].
- Probiotic supplements (containing *Lactobacillus acidophilus*): a healthy microbiome is essential for the management of endometriosis. There is a community of gut bacteria and specifically bacterial genes, called the estrobolome, that produce an enzyme supporting estrogen metabolism. Thus, probiotics can also be recommended for

maintenance of gastrointestinal and immune health. However, people who are severely immunocompromised or taking immune suppressive drugs should speak to their physicians before taking such supplements [42, 43].

- Lastly, broccoli, Brussels sprouts, oranges and grapefruit, cherries, apples, and spinach that are rich in calcium D-glucarate (the calcium component of D-glucaric acid, which is contained in these foods) can help rid the body of toxins and the body eliminate excess estrogen [44]. For endometriosis, calcium D-glucarate may relieve symptoms caused by too much estrogen. The recommended dose is suggested between 500 to 1000 milligrams one to three times daily [45]

DISCUSSION

There is ample evidence in the literature concerning the beneficial action of a number of natural nutrients that can activate mechanisms for altering and/or improving human health. However, since the definition of functional foods has not universally been regulated [14] and the effects obtained by the aforementioned “bioactive compounds” supplied either as commercial pharmaceutical preparations or taken up by simply eating “functional foods” seem advantageous and often miraculous in certain conditions, caution is advised when it comes to vitamin use. Vitamin-related toxicity is frequently observed; if taken incorrectly or in excess, vitamin uptake may be a potential health hazard [46]. Almost 60,000 instances of vitamin toxicity are reported annually to the United States (US) poison control centers. Due to their ability to accumulate in the body, fat-soluble vitamins have a higher potential for toxicity than water-soluble vitamins do. Iron-containing vitamins are the most toxic, especially in pediatric acute ingestions. Potential risks of inappropriate vitamin and supplement regimes include an increased risk of coronary heart disease, hypertension, thrombophlebitis, peripheral neuropathy, ataxia, neurological effects, liver toxicity, congenital abnormalities, gouty arthritis, jaundice, kidney stones, diarrhea and even spontaneous abortion [47].

CONCLUSION

As many patients show intolerance and/or allergic reactions against a number of chemical pharmaceutical compositions or their excipients, efforts focus on the use of naturally occurring substitute target-specific treatments with fewer side-effects. Under this prism, the up-to-date incurable condition of endometriosis needs to be meticulously explored since a remedial action may be achieved by targeting the MESC via the fortification of the immune system using bioactive compounds. Although there are reports analyzing possible operating modes of a load of naturally occurring nutrients [48], a 2018 review gives insight on the anti-inflammatory activities of certain medicinal plants from Africa [49], thereby opening a new window for the examination of immune parameters that, as in the present case, may be of importance. However, since there is a long way to go for the full exploration of all potential pathways a functional food may trigger or follow, it is imperative to undertake studies for investigating the action of these bioactive substances, particularly on the induction of the appropriate immune conditions that may, can, or will fortify the organism immunologically to intercept MESC at early stages for reversing the burden of the disease.

Abbreviations: Mesenchymal endometriotic stem cell, MESC; Endometriotic stromal cells, ESCs; Prostaglandin E, PGE; Coenzyme Q₁₀, CoQ₁₀; Diindolylmethane, DIM; T regulatory cells, Tregs; United States, US

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