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TRADITIONAL AND ORTHOMOLECULAR MEDICINE VERSUS DE MATERIA MEDICA IN TREATING ENDOMETRIOSIS

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ABSTRACT:

Endometriosis is an inflammatory, non-lethal, non-malignant, cancer-like disease as its diagnosis, course and stage determination exactly resembles cancerous states. According to latest theories, endometriosis is caused, inter alia, by a suppressed or incompetent immune system unable to eradicate the non-hemopoietic mesenchymal endometriotic stem cell (MESC) that escapes immune surveillance and, thus, migrates to and invades ectopic tissues. Thus, efforts focus on boosting immune parameters for, at least, minimizing the risk of the disease. Therefore, this short review discusses available approaches, such as those of traditional medicine using commercial formulations, orthomolecular medicine employing vitamin and mineral supplementation, as well as natural product administration based on the teachings of the first Pharmacopeia of Pedanius Dioscorides. These approaches share common pathways for pain alleviation and boosting immunity for potentially intercepting the MESC, thus reducing the risk and/or onset of the disease.

AN OVERVIEW OF THE DISEASE

Endometriosis, from the ancient Greek endo= inside, metra= womb and iosis= disease due to a virus, is an inflammatory, non-lethal, non-malignant disease. Although endometriosis is a benign disease, it shares many of the features of cancer cells as its course, diagnosis and stage determination exactly resembles cancerous states and can, thus, be viewed as a neoplastic process that, surprisingly, may show up on cancer imaging with positron emission tomography scanning giving a false positive scan. Endometriosis is characterized by the presence of ectopic endometrial implants and associated with infertility and pelvic pain. Its actual prevalence among the general population is difficult to ascertain, however estimates suggest that the reproductive health of as many as 3 to 10% of women are affected by this disorder [1, 2]. The first case was described more than 300 years ago and has since been accepted as a chronic, painful and, often, progressive disease in women. By definition, it concerns the migration, implantation, growth and function of endometrial tissue mainly to the peritoneum, on or next to the ovaries and less frequently to the cul-de-sac, uterosacral ligaments, fallopian tubes, vagina, urinary track (20% of cases) or even to the gastrointestinal tract (12-37% of patients) and, rarely, to the lungs, arms or thighs [3-5]. It is accepted that the rate of conception is reduced in women suffering from endometriosis [6, 7]. However, it is not yet known whether infertility is due to the endometriotic state of women or whether other endometriosis-associated factors lead to infertility. The proposed mechanisms for the development of infertility in endometriotic women include many gynecologic reasons that have already been extensively described [8-11]. Other causes include the use of chemicals, *Candida albicans* infection or abnormalities, while various observations show that endometriosis is a genetic and pre-determined disease due to environmental, endocrinological and immunological factors [12-15]. In addition to the above described theories, others suggest that endometriosis originates from the metaplasia of the coelomic epithelium [16]. This theory has gained substantial grounds as cells from both the peritoneum and endometrium derive from a common embryological precursor, the coelomic cell. Additionally, the Levander and Normann view [17] points to a combination of the Sampson's [5] and Meyer's [16] theories, whereas Batt and Smith suggest that the ectopic placement of endometrial cells occurs during the fetal life of a female embryo, where the cells that are programmed to form the endometrium stay outside the uterine wall and, therefore, endometrial cells are placed at a wrong position before a woman's birth [18]. These later theories have led Du and Taylor [19] to discover and investigate the non-hemopoietic mesenchymal stem cell (MESC) that, as proposed by Vassiliadis [20, 21], can escape surveillance due a frail immune system that is not competent enough to intercept this immaturely senescent cell that migrates to and invades ectopic tissues. However, this issue seems able to be resolved by the use of certain natural products [22-24] that may reverse endometriosis by fortifying the immune system to intercept the MESC. Therefore, natural products, that will be discussed below, were lent from the "De Materia Medica", the first ever Pharmacopoeia written by the Greek physician, pharmacologist and botanist Pedanius Dioscorides who lived during the first century BC and successfully employed a number of plants and extracts for treating various and serious gynecologic conditions [25]. These products are alleviating pain, boosting general immunity and, thus, appear excellent candidates for combating and/or reversing endometriosis by annihilating the MESC. Meganutrients used for the orthomolecular approach, on the other hand, have been shown 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, in turn may be a key factor in intercepting the MESC for preventing or correcting endometriosis. Lastly, pharmaceutical formulations of the traditional medicine can only regulate a woman's hormonal system and alleviate pain. Analytically:

TRADITIONAL MEDICINE

The World Health Organization (WHO) identifies traditional medicine as "the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" [26]. As there is no cure for endometriosis, however, treatments, according to the aforementioned definition, are only designed to relieve symptoms. Usually, non-steroidal anti-inflammatory drugs (such as ibuprofen), oral contraceptives and hormone-suppressing drugs (which stop ovulation) are first-line treatments for regulating hormones, slowing down the growth of endometrial implants and

decreasing menstrual flow. The most common conventional treatments include:

(i) **Lupron® (a GnRH agonist)** used to induce a hormonal and menstrual suppression in patients with endometriosis, resulting in alleviation of pain symptoms [27]. However, its administration is often accompanied by side-effects, including decreased blood pressure, redness, pain and burning at the sight of injection, fatigue, headache, upset stomach and muscle aches.

(ii) **Progestins** that behave like the female hormone progesterone and work by suppressing the growth of endometrial impacts and reducing endometriosis-induced inflammation in the pelvic cavity. During treatment, women lose their periods and ability to conceive. Women who have had long-acting injections may experience prolonged delays in the return of menstruation after treatment. Like all hormone medications, there are some common side-effects, including acne, bloated stomach, bleeding, breast discomfort, depression, fatigue, headaches, upset stomach, nausea, vomiting and weight gain. These side-effects can be difficult to live with and some women cannot complete a course of treatment because they find them intolerable [28].

(iii) **Danazol® (7alpha-ethinyl testosterone)** is a synthetic steroid that serves as a mild androgen (hormones produced by the male testes) but has no estrogenic or progestational properties. Androgens are responsible for the functioning of the male reproductive system and the development of male characteristics, such as facial hair and a deep voice. Danazol® is used to suppress the growth and development of endometrial tissue. The hormonal environment caused by Danazol® stops menstruation as well. Because it serves as a synthetic male hormone, Danazol® has androgenic side-effects, such as weight gain, increased body hair and acne, decrease in breast size, deepening of the voice, water retention, as well as oily skin or hair [29].

ORTHOMOLECULAR MEDICINE

The term "orthomolecular" was first utilized by the two-time Nobel Laureate Linus Pauling in 1968 [30] to characterize the treatment of disease with nutrients that are endogenous to the human body. 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, particularly calcium, vitamin C and zinc for example, 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 is another form of alternative medicine aiming to maintain human health through nutritional supplementation [31]. The first megavitamin therapy report 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. In the same year, he also showed that vitamin C could inactivate diphtheria toxin, whereas the first report on endometriosis came out in 1940 by the Shute brothers (as reported by Andrew Saul) revealing that vitamin E prevents endometriosis [32].

Briefly, concerning endometriosis, a number of vitamins, supplements and/or trace elements can be mentioned as their role on endometriosis, as a whole, has been described, i.e. on endometriotic lesions, fertility, pain, hormonal and/or immune regulation. Their action, with the partial exception of resveratrol shown to inhibit development of experimental endometriosis in vivo and reduce endometrial stromal cell invasiveness in vitro (see below), however, has never been examined in relation to inducing the proper conditions for intercepting the MESC at early stages, thus reversing the burden of the disease.

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 PGE1, helping to manage painful symptoms. In addition, a 2014 study by Herington et al., using an experimental mouse model of endometriosis, showed that in mice with a 10% supplemented fish oil diet, adhesion score and disease burden were significantly reduced [33].

Melatonin has anti-cancer and anti-inflammatory properties as studied by Guney et al., in 2008, in a mouse model of endometriosis. The authors found that melatonin causes regression and atrophy of the endometriotic lesions in experimental mice [34].

Medicinal cannabis. As endometriosis is a benign disease usually responding to natural substances with anti-cancer activity, then one would expect cannabis sativa extract (β-caryophyllene constituent of essential oil of *Cannabis sativa*) to have beneficial effects like suppression of the growth of endometriotic implants by 52.5% compared with controls when used at 10 mg/kg. Also β-caryophyllene produced apoptosis in luminal epithelium of the cyst, as well as in endothelial cells of blood vessels [35]. An additional benefit, reduction in endometriosis-associated pain, was also reported [36].

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.

Coenzyme Q10 (CoQ10) is suggested as an antioxidant and for immune support. Studies on endometriosis, however, are lacking.

Resveratrol is a natural substance obtained from red wine that has anti-proliferative and anti-inflammatory properties [37]. A 2011 study by Brune-Tran et al. showed that resveratrol inhibits development of experimental endometriosis in vivo and reduces endometrial stromal cell invasiveness in vitro [38]. 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 natural occurring supplement.

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 [39]. In marked contrast, 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. Thus, the use of this nutrient by young women may be a potential risk factor responsible for the onset of endometriosis at a later stage of their lives [40].

Iron (clams, fortified cereals, liver, oysters, lean red meat, dried beans) prevents anemia, weakness and fatigue due to heavy bleeding. Women with endometriosis tend to have very heavy periods which can lead to an iron deficiency. This can lead to anemia, which is characterized by extreme fatigue and weakness.

Magnesium (bananas, barley, green beans, kelp, sunflower seeds, 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. It is also a muscle relaxant decreasing cramping.

Selenium (cabbage, celery, cucumbers, Brazil nuts, tuna, cod, 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. 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.

Zinc (ginger root, oysters, lamb chops, pecans) is critical for proper thymus gland and immune system function. Research has shown that daily intake of 30 mg of zinc reactivate 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.

Vitamin A (apricots, broccoli, cantaloupe, carrots, eggs, milk, pumpkin, spinach, squash) improves the immune system; is an antioxidant; helps lessen profuse menstrual bleeding.

Vitamin B complex (fortified cereals, beans, red meat, poultry, mollusks, liver) helps break down proteins, carbohydrates and fats in the body; helps keep estrogen levels naturally low; helps produce good prostaglandins. 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, which will help many sufferers. The B vitamins are also crucial for the conversion of essential fatty acids into beneficial prostaglandins having a relaxing effect on the womb muscles and anti-inflammatory properties.

Vitamin C (berries, broccoli, cantaloupe, grapefruit, lemons, oranges, peppers, spinach, strawberries) helps boost the immune system and fight off disease; is an antioxidant; helps control excessive bleeding; detoxifies pollutants.

Vitamin E (almonds, avocado, eggs, safflower oil, salmon, sunflower oil) is known to ensure that animals have healthy uterine linings and it has been used by farmers since the 1930's. It improves the immune system and, in endometriosis, has been shown to relieve menstrual cramps in 70 percent of women within two menstrual cycles.

Beta carotene (carrots, spinach, sweet potatoes, tomatoes, cantaloupe) increases the number of infection-fighting cells, natural killer cells and helper T-cells, as well as being a powerful antioxidant that mops up excess free radicals that accelerate ageing. It also converts to vitamin A in the body.

Probiotic supplement (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 that supports the metabolization of estrogen. Thus, probiotics can also be suggested when needed for maintenance of gastrointestinal and immune health. People who are severely immune compromised, or who are taking immune suppressive drugs, however, should speak to their physicians before taking probiotic supplements.

Last, but not least, **calcium d-glucarate** can help rid the body of toxins and may help the body get rid of excess estrogen. For endometriosis, calcium d-glucarate may relieve symptoms caused by too much estrogen. The University of Maryland Medical Center recommends taking 500 to 1,000 milligrams of calcium d-glucarate one to three times daily.

Nevertheless, a word of caution is advised when it comes to vitamin use since vitamin-related toxicity is frequently observed as, if taken incorrectly or in excess, vitamin uptake may be a potential health hazard [41]. Almost 60,000 instances of vitamin toxicity are reported annually to US poison control centers. Owing 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, spontaneous abortion, gouty arthritis, jaundice, kidney stones and diarrhea [42].

THE DE MATERIA MEDICA APPROACH

Since the first Pharmacopoeia under the title "De Materia Medica", the importance of the utilization of plants and herbs has been an invaluable medicinal tool successfully employed for strengthening the immune system for combating a number of diseases in general or assisting fertility and reproductive issues in particular. The beneficial use of herbal extracts, constituting the basis of modern medicines, is being viewed upon the action possibly provided on the mesenchymal endometriotic stem cell causing endometriosis. Thus, according to the first ever Pharmacopoeia there is a number of plants and extracts that have been successfully employed for treating various and serious gynecologic conditions [25]. Among them, there is special mention on the use of the alfalfa and/or red clover, containing plant estrogens and isoflavones, prescribed for women suffering from endometrial hyperplasia, while mastika and/or its oil was used for alleviating pelvic pains since, as it is known today, mastika diminishes the production of vascular endothelial growth factor inhibiting the proliferation of the cells of the vascular endothelium in vitro, as well as in vivo [43]. In addition, although in the Hippocratic oath there is mention for the avoidance of abortion due to medical, ethical and personal issues, during the seventh century BC controlled abortion was supported by the ancient Egyptians and later by the Greeks using silphium, a member of the giant fennel family used for contraception, a treatment used abundantly by the famous gynecologist-obstetrician Soranus from Ephesus and the ancient herbalist/physician, Dioscorides [44]. It is worth of mentioning that even though silphium was eradicated due to its massive use, it was replaced by the similarly active *fetid* horehound, *Mentha pulegium* (pennyroyal), absinthe, *Commiphora molmol and Ruta graveolens* or commonly named rue [45].

Similarly, a number of plants and extracts, used alone or in combination with other natural products, have been described by Dioscorides as suitable for the strengthening of the immune system to combat streptococcal and viral infections, inflammations, edemas and arthritis problems. Thus, in his great Greek herbal "Peri Ylis Iatrikis" (Latinized as "De Materia Medica"), there is mention on the beneficial action of many herbs, plants, trees and roots on the above named and related to immunity conditions [25]. Some representative restorative for the immune system elements found in Dioscorides' work included valerian, nard, hazelwort, chestnut, Alexandrian senna, cardamom, saffron crocus, bitter and/or sweet almond, laurel, oil of fenugreek, lily, henna shrub, Egyptian privet, iris oil, oriental plane, coarse myrrh, pines, pine cones, savin, cedar of Lebanon, oil of cinnamon, olibanum resin, cypress, cane, bamboo, gooseberry, rose, acacia, oil tree, pickled olives, walnut, garlic, wild rhubard, yellow gentian, bachelor's button, mabberley, winter-sweet marjoram, pennyroyal, pudding grass, white dittany, potherb thyme, wild trefoil, king's clover, herb of grace, cumin, coriander, tormentil, holly herb, psyllium, lily of the valley (ephemeron), mother of thousands (helxine), water lettuce, mullein (phlomos), black sesame, indigo plant, ochre, stinkwort, old wine with honey, vinegar honey, thyme vinegar, sediment of wine and/or vinegar, grape wine and many more.

Some of the herbs that can be used in endometriosis as anti-inflammatory or pain killers include:

Chasteberry (*Vitex agnus castus*). Although not significantly investigated, preliminary studies have shown that extracts of *Agnus castus* can stimulate the release of leutenizing hormone (LH) and inhibit the release of follicle stimulating hormone (FSH). *Agnus castus* may also decrease excessive prolactin levels, an action that may help infertile women [23].

Evening primrose oil (*Oenothera biennis*) or **Borage oil** is used as a source of gamma linolenic acid (GLA) for symptoms of hormonal imbalance and stress. GLA is actually converted into prostaglandins that work against the pain-causing prostaglandins (PGE1 versus PGE2). Strong anti-inflammatory properties and effectiveness in arthritis, pre-menstrual syndrome and skin conditions have been described.

Silybum marianum. Milk thistle contains the antioxidant silymarin repairing the cells in the liver and protecting cells from damage (thereby regenerating the strength of the liver to detox the body of excess estrogen). It also has a strong anti-inflammatory function, thus making it a powerful herb for endometriosis.

Also, for pain alleviation and inflammatory conditions, Bromelain (*Ananus comosus*) and **Turmeric (*Curcuma longa*)** have been suggested. However, both may cause serious adverse events as they may increase the effect of blood thinning medications, such as warfarin (Coumadin®).

Lastly, a non-herbal natural product, **oleocanthal**, contained in extra virgin olive oil, displays a similar structure to the molecule ibuprofen, thus being only able to alleviate the endometrial pain via, possibly, cyclooxygenase inhibition [46]. Its action, however, may be extended to a further therapeutic level since this substance beneficially affects inflammatory conditions [47] as the case with endometriosis is.

In marked contrast, when it comes to correcting endometriosis by attacking the endometriosis-causing MESC (see above "An Overview of the Disease") via the fortification of an incompetent to surveillance immune system, significant research results have revealed a number of natural products that show beneficial action for fighting and/or confronting many diseases via the strengthening of the immune system [48] and several conditions dealing with fertility and reproductive issues [49]. Special attention has been paid on the remedial action pine bark extracts (Pycnogenol®), almond skins, *Agaricus Blazei* murrill and oleuropein may have on a destabilized organism that fails to combat illness by its own, which extrapolates to the endometriotic state that needs to fight the MESC.

The **French maritime pine bark extract** comes from the bark of *Pinus pinaster* growing on the coast of Bordeaux, France. The extract is presently used worldwide as a nutrition supplemental food under the name of Pycnogenol® [50]. The pharmacological mechanism of the extract has, inter alia, a positive action on dysmenorrhea and endometriosis [51].

Almond skins are one of the most known natural extracts that possess health-promoting activities. They provide strong anti-oxidant, antimicrobial plus a number of beneficial prebiotic properties and, also, immunomodulatory and antiviral actions via interleukins (IL-4, -10, -12), interferon-α and tumour necrosis factor-α, which are integral part of the endometriotic pathway [52].

Mushrooms and primarily basidiomycetous fungi are popular and valuable foods, low in calories and high in essential amino acids, vitamins, minerals and fibers. Specifically, the mushroom of the Gods, the well-known *Agaricus Blazei* murrill, has been recognized as a potential cure since it possesses many beneficial therapeutic functions. In the context of cancer-like and cancerous states, especially of endometrial origin, their action improves inflammatory conditions, natural killer cell activity and quality of life [53].

Finally, the remedial properties of **oleuropein** from olive leaves are known since 1908 and found to influence positively the immune system [54]. The fact that oleuropein has been shown, inter alia, to have a potent anti-inflammatory action [55], makes such an extract an attractive candidate for the study of the fortification of the immune system vis-à-vis the invading MESC since endometriosis is a *bona fide* inflammatory disease. To this end, a number of pharmaceutical compositions containing oleuropein have been patented [56].

CONCLUSIONS

With the exception of the traditional medicine that only regulates hormonal imbalances and alleviates pain, the orthomolecular and De Materia Medica approaches appear more promising for successfully strengthening the immune system towards a curative outcome in endometriosis. The underlying mechanisms, however, behind the action of the aforementioned products and/or their bioactive ingredients are numerous, mostly speculative and, thus, remaining under scrutiny. For this, it is imperative to undertake studies for investigating the induction of the appropriate immune conditions that can or will fortify the organism to intercept the MESC at early stages for reversing the burden of the disease.

CONFLICTS OF INTEREST

The Authors declare no conflict of interest in regard to this study.

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