Potential advantages of medicinal plants over pharmaceutical compositions in endometriosis through the fortification of the mesenchymal endometriotic stem cell

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ABSTRACT

Intolerance and/or allergic reactions to a number of chemical pharmaceutical compositions or their excipients underlie the need for the use of natural products in the medical field. Therefore, efforts should be focused on naturally occurring substitute target-specific treatments, especially medicinal plants, with fewer side-effects. A condition that seems to benefit from such an approach is endometriosis, an incurable, inflammatory, non-lethal, non-malignant, cancer-like disease, which, inter alia, is caused by an incompetent or suppressed immune system unable to eliminate the non-hemopoietic mesenchymal endometriotic stem cell (MESC) that escapes immune surveillance and, thus, migrates to and invades ectopic tissues. As opposed to many medicinal plants that can reverse the course of the disease by fortifying the patients’ immune system rendering it capable of intercepting the MESC, current available pharmaceutical compositions can only alleviate pain and/or inflammation.

Key words: Endometriosis, mesenchymal endometriotic stem cell (MESC), immune system, medicinal plants, de materia medica.

INTRODUCTION

Endometriosis is an inflammatory, non-lethal, non-malignant, cancer-like disease having a diagnosis, course and stage determination that exactly resemble cancerous states (Simpson et al., 1980). According to latest theories, endometriosis is caused by the host’s own immune system that is unable, either suppressed or incompetent, to eradicate the non-hemopoietic MESC that escapes surveillance (Vassiliadis, 2011, 2012). Therefore, the disease is initiated as there are no physical barriers to stop the spreading of MESCs to ectopic tissues. It, thus, appears reasonable to consider that boosting immunity may be the appropriate way to proceed against endometriosis. As it is known from the ancient times, immunity can effectively be enhanced by the use of natural products, as described in the first Pharmacopeia of Pedanius Dioscorides since the first century BC (Osbaldeston, 2000), as well as, vitamin and mineral supplementation known as orthomolecular medicine (Braverman, 1979), an approach that is under intense scrutiny due to contradicting results but, nevertheless, meriting attention. Although vitamins and minerals are offered as commercial pharmaceutical compositions, they do not fall, by and large, into the real medicinal family of remedies like most other drugs that target disease. As a result, traditional medicine has no artillery to assist the immune system to becoming functional against the interception of the specific intruder called MESC. Since the weapons of traditional medicine for endometriosis are only for easing pain and inflammation, this blank can be successfully filled by a wide range of medicinal plants that also, nowadays, make part of a number of commercially available supplements with well-accepted potential.
**ENDOMETRIOSIS**

Endometriosis, according to the ancient Greek endo= inside, metra= womb and iosis= disease due to a virus, is an inflammatory, non-lethal and non-malignant disease, resembling cancer according to its mode of diagnosis and stage determination. It is characterized by the presence of ectopic endometrial implants and associated with infertility and pelvic pain having a high prevalence among the general population (Simpson et al., 1980; Panidis and Matalliotakis, 1998). Although the first case was described more than 300 years ago, endometriosis remains an incurable, chronic, painful and, often, progressive disease that starts with the migration, implantation and growth of endometrial tissue to the peritoneum, on or next to the ovaries and, less frequently, to the cul-de-sac, uterosacral ligaments, fallopian tubes, vagina, urinary track or even to the gastrointestinal tract and, rarely, to the lungs, arms or thighs (Ivanoff, 1898; Halban, 1925; Sampson, 1927). Endometriosis is marked by reduced conception (infertility) (D’Hooghe et al., 2003; Gianetto-Berrutti and Feyes, 2003), which may be attributed to other factors as well, such as gynecologic reasons (Summario et al., 1998; Halis and Arici, 2004; Senturk and Arici, 1998; Vassiliadi et al., 2005), use of chemicals, Candida albicans infection, genetic predisposition, environmental conditions, endocrinological problems and immunological parameters (Furuya et al., 2005; Vinatier et al., 1996; Crisp et al., 1998; Stefansson et al., 2002). Although the aforementioned causes have well been documented, other theories suggest that endometriosis originates from the metaplasia of the coelomic epithelium (Meyer, 1919), a concept that gained substantial grounds as cells from both the peritoneum and endometrium derived from a common embryological precursor, the coelomic cell.

A combination of other theories, however, suggest that the ectopic placement of endometrial cells occurs during the fetal life of a female embryo, where the cells, programmed to form the endometrium, stay outside the uterine wall and are placed at a wrong position before a woman’s birth (Levander and Normann, 1955; Batt and Smith, 1989). Further work led Du and Taylor (2007) to discover a non-hemopoietic mesenchymal stem cell (MESC), which, as proposed (Vassiliadis, 2011; 2012), can escape surveillance due to a frail immune system that is not competent enough to intercept this immaturely senescent cell allowing it to migrate to and invade ectopic tissues (Vassiliadis, 2010; 2013; 2015).

As briefly analyzed and opposed to natural products used since the ancient times (Osbaldeston, 2000), current available commercial pharmaceutical compositions of the traditional medicine can only regulate a woman’s hormonal system and alleviate pain being, thus, totally incapable to act on the patients’ immune system as to render it competent to fight the MESC for reversing the burden of the disease.

**COMMERCIAL PHARMACEUTICAL COMPOSITIONS**

Although the World Health Organization 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” (WHO, 2008), endometriosis remains incurable. The available commercial treatments are only designed to relieve symptoms. Among them, non-steroidal anti-inflammatory drugs, such as ibuprofen, as well as, oral contraceptives and hormone-suppressing drugs that stop ovulation, are considered 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, mainly used to induce hormonal and menstrual suppression in endometriotic subjects, thus, resulting in alleviation of pain symptoms (Schweppe and Hummelshoj, 2005). Its administration is often accompanied by mild side-effects, including decreased blood pressure, redness, pain and burning at the sight of injection, fatigue, headache, upset stomach and muscle aches;

(ii) Progestins act like the female hormone progesterone, thus, suppressing the growth of endometrial impacts and reducing endometriosis-induced inflammation in the pelvic cavity. Treatment often leads to loss of menstrual periods and infertility. Long-term treatment may lead to prolonged delays in the return of menstruation. Like all hormone medications, progestins may cause some common, but often intolerable, side-effects, including acne, bloated stomach, bleeding, breast discomfort, depression, fatigue, headaches, upset stomach, nausea, vomiting and weight gain (Kistner, 1958).

(iii) Danazol® (7alpha-ethyl testosterone), used to suppress the growth and development of endometrial tissue, is a synthetic steroid serving as a mild androgen having, however, no estrogenic or progestational properties. The hormonal environment caused by Danazol® stops menstruation as well. Since it serves as a synthetic male hormone, this medication has androgenic side-effects like weight gain, increased body hair and acne, decrease in breast size, deepening of the voice, water retention, as well as, oily skin or hair (Biberoglu and Behrman, 1981).

**MEDICINAL PLANTS**

The medicinal plants that will be discussed in this section, are lent from the "Peri Ylis Iatrikis" (Latinized as "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, constituting the basis of modern medicines, for strengthening the immune system for combating a number of diseases in general or assisting reproductive and various gynecologic conditions (Osbaldeston, 2000).

Among them, there is special attention on the use of the alfalfa and/or red clover, containing plant estrogens and isoflavonones, 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 (Loutrari et al., 2006). In addition, although in the Hippocratic oath the avoidance of abortion due to medical, ethical and personal issues was mentioned and 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 was used for contraception, a treatment used abundantly by the famous gynecologist-obstetrician Soranus from Ephesus and the ancient herbalist/physician, Dioscorides (Osbaldeston, 2000; Riddle, 1994). It is important to note that, even though silphium was eradicated due to its massive use, it was successfully replaced by the similarly active fetid horehound, Mentha pulegium (pennyroyal), absinthe, Commiphora molmol and Ruta graveolens or commonly named rue (Voth, 1989).

It is also worth mentioning that a number of plants and extracts have been described by Dioscorides as suitable for the fortification of the immune system to combat streptococcal and viral infections, inflammations (as the case of endometriosis), edemas and arthritis problems. Thus, the beneficial action of many herbs, plants, trees and roots towards to immunity-related conditions was also reported (Osbaldeston, 2000). These include 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, picked olives, walnut, garlic, wild rhubarb, yellow gentian, bachelor's button, madder, 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 (ephemerom), mother of thousands (hekine), water lettuce, mullein (phlomos), black sesame, indigo plant, ocher, stinkwort, old wine with honey, vinegar honey, thyme vinegar, sediment of wine and/or vinegar and grape wine etc (Voth, 1989).

It is, thus, obvious that for endometriosis, in particular, the beneficial use of herbal products/extracts will be herein viewed upon the action possibly provided through the strengthening of the immune system, either as anti-inflammatory agents (and to a lesser degree pain killers), similar to the commercial pharmaceutical formulations as previously discussed, or potent mediators against the disease itself.

For the anti-inflammatory and/or pain killing action of these medicinal products the following have been described:

- Chasteberry (Vitex agnus castus) extracts of Agnus castus, which, although not significantly investigated, 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 found helpful in infertile women (Vassiliadis, 2013);
- 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 acting against the pain-causing prostaglandins (PGE1 versus PGE2). Strong anti-inflammatory properties and effectiveness in arthritis, pre-menstrual syndrome and skin conditions have also been attributed (Lam and Lam, 2017);
- Milk thistle (Silybum marianum) contains silymarin, an antioxidant repairing the cells in the liver and protecting cells from damage, regenerates the strength of the liver to detox the body of excess estrogen. Strong anti-inflammatory function, that makes it a powerful herb for endometriosis, has also been reported (Lam and Lam, 2017);
- Bromelain (Ananus comosus) and Turmeric (Curcuma longa) have been suggested for pain alleviation and relief of certain inflammatory conditions (Eastwood, 2003). However, both may cause severe adverse events since they are capable of increasing the effect of blood thinning medications (Herington et al., 2013).
- Lastly, oleocanthal, contained in extra virgin olive oil, displays a similar structure to the molecule ibuprofen, thus, being only able to alleviate the endometrial pain through possibly, cyclooxygenase inhibition (Beauchamp et al., 2005). Since oleocanthal beneficially affects inflammatory conditions (Parkinson and Keast, 2014), its use may be extended to a further therapeutic level concerning endometriosis, a bonafide inflammatory disease.

Control of inflammation and pain, however, does not cure endometriosis. The disease, as already discussed, remains incurable and correcting it seems only possible by attacking the aforementioned-described endometriosis-causing MESC through the fortification of an incompetent to surveillance immune system.

To this end, significant research results have revealed a number of naturally occurring products exhibiting beneficial action for fighting and/or confronting many diseases through the strengthening of the immune system (Vassiliadis, 2013; Lindner, 1976; Sloan, 2002). Specifically, particular 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.

In a nutshell, 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 Pycnogenol® (Rohdewald, 2002). The pharmacological mechanism of the extract exhibits, *inter alia*, a positive action on dysmenorrhea and endometriosis (Kohama et al., 2007).

Almond skins are one of the most known natural extracts with health-promoting activities. They provide strong antioxidant, antimicrobial properties including a number of beneficial prebiotic properties and, also, immunomodulatory and antiviral actions through interleukins (IL-4, -10, -12), interferon-α and tumour necrosis factor-α, all of which are integral part of the endometriotic pathway (Sang et al., 2002).

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 *A. Blazei* murrill, also known as the mushroom of the Gods, has been accepted 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 (Mattila et al., 2002).

Finally, the curative properties of oleuropein from olive leaves, known since 1908, are positively influencing the immune system (Bourquelot and Vintilesco, 1908). The fact that oleuropein has been shown, among others, to have a potent anti-inflammatory action, makes such an extract a considerable candidate for the study of the fortification of the immune system with regard to the invading MESC (Ryu et al., 2015). To this end, a number of pharmaceutical compositions containing oleuropein have been patented (Raederstorff et al., 2010).

**CONCLUSION**

Fortification of the immune system may be achieved with the use of many naturally occurring products that fall under the general term of “Medicinal Plants”. Although the underlying mechanisms behind the action of the earlier mentioned natural bioactive ingredients appear numerous and speculative, some of their effects have been documented since the ancient times. In this review, the remedial effect of certain medicinal plants for controlling endometriosis has been discussed focusing on targeting the MESC through the fortification of an incompetent immune system.

The available scientific literature shows that, in contrast to common pharmaceutical compositions of the traditional medicine that only regulate hormonal imbalances and alleviate pain, the use of medicinal plants appears more promising for successfully strengthening the immune system towards a curative outcome. It is, however, absolutely necessary to undertake studies for investigating the induction of immune pathways that can or will fortify the organism to intercept the MESC at early stages for reversing the burden of the disease.

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