

## **Immune and homeostatic surveillance are positively modulated in cancer-like and cancer conditions by a number of natural products**

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### **ABSTRACT**

Endometriosis, a non-lethal cancer-like inflammatory condition, and cancer share many common features. These shared features include the inability of the human body to confront the cause of disease initiation, due to incompetent immune and homeostatic surveillance. Additionally, both diseases can be detected using the same diagnostic tools. Moreover, alternative, non-chemical treatment can be successfully achieved by a number of common substances found in nature that can fortify the human body to combat disease. Therefore, this commentary focuses on and discusses how remedial action pine bark extracts (Pycnogenol<sup>®</sup>), almond skins, *Agaricus Blazei murrill*, oleuropein and oleocanthal may have positive benefits for a destabilized organism which has failed to combat illness by its own efforts. The selection of the natural products discussed within this article has been accomplished via a thorough literature search. Although this article focuses on maintaining the two key processes of immune and homeostatic surveillance, more systems should be further investigated for reaching definite and credible conclusions.

**Key Words:** Surveillance, homeostasis, endometriosis, cancer, natural products

### **INTRODUCTION**

Numerous processes interact in harmony to protect the human body from disease. Among these processes, two are of particular significance: immune surveillance, the recognition of foreign antigens and other harmful invaders, and homeostatic surveillance, a multipurpose line of physiological checks which maintains the body's parameters within a normal range of values. As these two systems protect the body from illness, it is relevant to discuss how to maintain these systems. However, this article will discuss and promote the natural method of using non-chemical substances to promote these systems' health. As nature offers ample protection through its well-organized biological system, organisms that receive and use nature's gifts function properly and maintain known biochemical processes running smoothly. Consequently, bodily intruders can be annihilated and health issues may be restored.

From the time of creation, man has used health laws, which first appeared in the Holy Bible [1], to stay in good physical shape and promote longevity of life. However, throughout the

centuries, adaptation to different lifestyles has also been accompanied by the development of a number of incurable diseases. As some of these diseases originate from within the human body, they have also led to the weakening of surveillance systems properties.

Based on a meticulous in length literature search with limited focus, this brief commentary will discuss how the human body may improve its health through the use of certain natural products. The destabilization of our own surveillance system involves two different issues that, although different, share common characteristics from diagnosis to treatment. The first is cancer and the second is a cancer-like condition, endometriosis, both of which follow almost identical pathways of progression [2].

### **Similarities and differences of the two disease states**

Endometriosis is considered a benign, non-life-threatening disease which is accompanied by severe abdominal pain and infertility [2, 3]. Like cancer, endometriosis has different stages of severity, which thereby makes its cure and treatment complicated and debatable [4]. Although the possibility that endometriosis can develop into a form of cancer has been questioned with little success since 1925 [5, 6], women with endometriosis have been shown to be more susceptible to cancers [7-9]. As discussed elsewhere [10, 11], this susceptibility demonstrates defective immune surveillance, due to mal-nutritive caloric restriction [12, 13] and immature senescence [11, 14] of the endometriosis-initiating non-hemopoietic mesenchymal endometriotic stem cells (MESC), which thereby prevents the immune system from annihilating cancerous cells. As reviewed extensively [11], the aforementioned immune surveillance theory was first conceptualized in the early 1900s by Paul Ehrlich [15]. He suggested that cancer cells frequently arise in the body but are recognized as foreign and eliminated by the immune system. Some 50 years later, Williams and Thomas suggested that the cell-mediated branch of the immune system evolved to patrol the body and eliminate cancer cells [16]. According to these concepts, tumors arise only if cancer cells are able to escape immune surveillance, either by reducing their expression of tumor antigens or by impairing the immune response to these cells.

The main differences between cancer-like endometriosis and cancer lie on the initiation phase and the end-point of both diseases, which are non-lethal and lethal, respectively. Endometriosis parallels cancer's patterns of migration and invasion, starting from a non-hemopoietic MESC [14]. In contrast, cancer cases originate from mature cells which, genetically or otherwise, multiply uncontrollably and finally metastasize in various organs. In both cases, the immune system appears and is clearly unable to combat either the MESC or cancerous spreading. Immune surveillance and homeostatic processes are shut off and aggravation prevails.

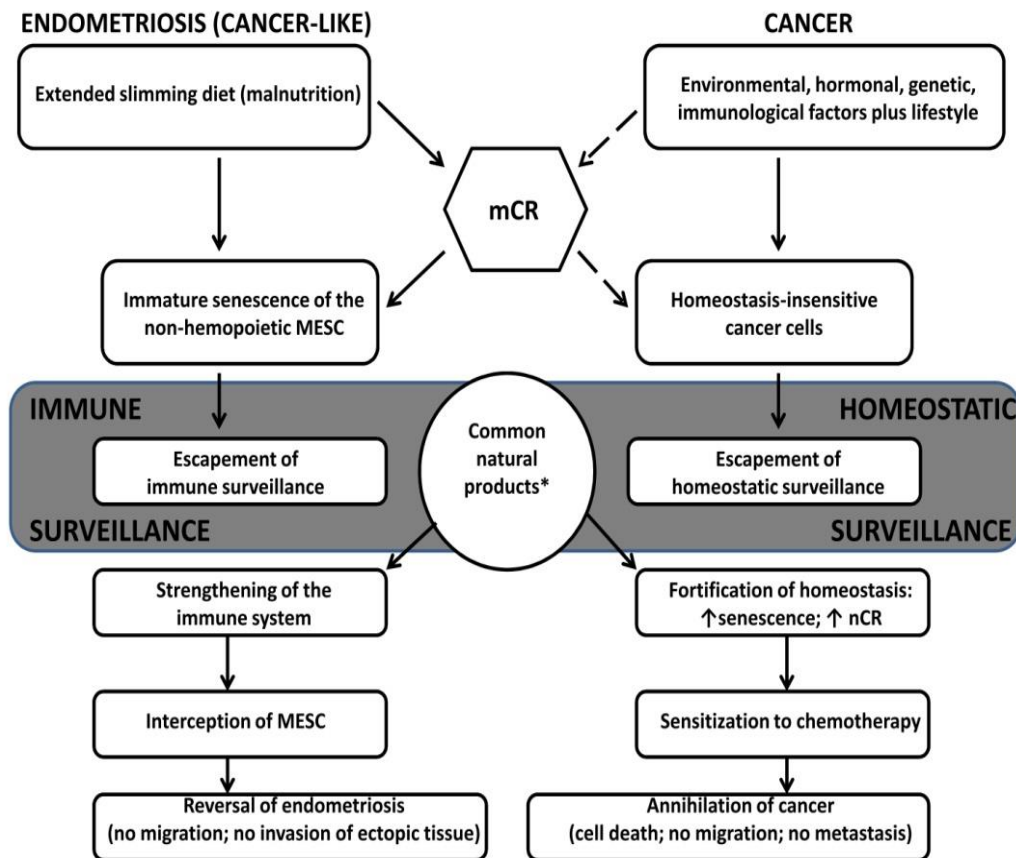
Diagnosis is accomplished by a battery of cell markers and secreted factors that are common in both diseases [18, 19], as well as genetic markers, seen in the case with the mutational analysis of BrCA1, BrCA2 and p53 is [20]. This list has continued to expand. For example, carcinoembryonic antigen, a new diagnostic marker, CYFRA 21 (cytokeratin 19), has been included in this list [21, 22].

### **Treatment approaches by natural products**

The major difference between cancer-like endometriosis and a cancerous state is treatment, as the former condition is incurable, with all available treatments being focused only on pain

alleviation. On the other hand, cancer treatments are numerous and accompanied by surgery and/or various forms of radiotherapy. Nevertheless, many reports exist which makes it clear that a number of natural products may have curative impact on a number of conditions [24, 25], products which have been established since the first Pharmacopoeia, written by the Greek physician, pharmacologist and botanist Pedanius Dioscorides, who lived during the first century BC [23], the Hippocrates era (fifth century BC) and within Eastern medicine. Although today's research reveals the pathways of action for these old herbal remedies, this article focuses on natural substances that can improve crippled immune systems and fortify patient's homeostatic or surveillance mechanisms, enabling these patient's to effectively combat illness. Between extensive lists of natural biologicals, our literature search revealed five natural products with a documented remedial action on both endometriosis and cancer. Therefore, this commentary focuses on the beneficially impact of pine bark extracts (Pycnogenol®), almond skins, *Agaricus Blazei murrill*, oleuropein and oleocanthal, briefly discussing their effects on a destabilized organism which cannot properly combat disease by itself.

As shown in Figure 1, the senescent immature MESC in endometriosis (left sequence of events) impairs immune surveillance by allowing the endometriotic stem cell to migrate [26].



**Figure 1.** Portrayal of events preventing endometriosis and cancer by the use of natural products.

CR, caloric restriction; mCR, mal-nutritive caloric restriction; nCR, nutritive caloric restriction; MESC, mesenchymal endometriotic stem cell. Solid arrowed lines represent referenced pathways; broken arrowed lines represent possible pathways; \*refers to Pycnogenol<sup>®</sup>, almond skins, *Agaricus Blazei* murrill, oleuropein and oleocanthal.

Additionally, the mature homeostasis-insensitive cancer cell (right sequence of events) is able to escape homeostatic surveillance. They can, however, be affected by the beneficial action of the aforementioned products, which acts in both endometriosis and cancer. These products can restore a destabilized organism's immune and homeostatic surveillance through the fortification of their respective frail systems.

One of these effective products include the French maritime pine bark extract, which 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<sup>®</sup> [27]. The pharmacological mechanism of the extract has a positive action on dysmenorrhea and endometriosis [28, 29], as well as on breast cancer [30] and other oncologic states [31].

Almond skins are one of the most well-known natural extracts that possess health-promoting activities. They provide strong anti-oxidant [32], are antimicrobial, and also contain a number of beneficial prebiotic properties [33] which also include immunomodulatory and antiviral actions through interleukins (IL-4, -10, -12), interferon- $\alpha$  and tumour necrosis factor- $\alpha$  [34], integral parts of the endometriotic [26] and cancerous pathways [35].

Mushrooms and primarily basidiomycetous fungi are popular and valuable foods, low in calories and high in essential amino acids, vitamins, minerals and fibers [36]. Specifically, the well-known *Agaricus Blazei* Murrill (ABM), known as the mushroom of the gods, has been recognized as a potential cure because it possesses many beneficial therapeutic functions. In the context of cancer-like and cancerous states, especially those of endometrial origin, their action improves inflammatory conditions, natural killer cell activity and quality of life in gynecological cancer patients undergoing chemotherapy [37]. Prostate cancer has also been effectively treated through the use of mushroom mycelium extracts [38].

The remedial properties of oleuropein [39] from olive leaves have also been known since 1908, having been discovered to positively influence the immune system [40]. This natural extract has documented anti-cancerous properties [41-43], which can be used to fortify the organism against various types of cancer. Because oleuropein has been shown, to have a potent anti-inflammatory action [44], this extract is an attractive candidate for the study of the fortification of the immune system vis-à-vis the invading MESC, since endometriosis is an inflammatory disease. To this end, a number of pharmaceutical compositions containing oleuropein have been patented [45], as this active ingredient has been shown to be capable of fighting and/or preventing inflammatory disorders [44].

Finally, oleocanthal, which is contained in extra virgin olive oil, displays a similar structure to the molecule ibuprofen. Olerocanthal is capable of alleviating endometrial pain, potentially through cyclooxygenase inhibition [46, 47]. However, these effects may be extended to a further therapeutic level, since this substance has been effectively used to treat inflammatory conditions [48, 49]. Importantly, oleocanthal has been reported to successfully control metastatic breast and prostate cancers [50].

Although the use of these natural products successfully fortifies both immune surveillance in endometriosis and homeostatic surveillance in cancer, the underlying mechanisms behind the action of the above natural products and/or their bioactive ingredients are numerous and mostly speculative; thus, these products and their effects should remain under scrutiny. For example, a point that merits further investigation is a possible differential action of these products when used in combination, or even when administered together with standard known medication. Due to the lack of these kinds of trials for the specific products discussed in this commentary, there are no currently available results on additive, synergistic or contrary effects.

## CONCLUSION

There is no doubt that Mother Nature can provide resources that can benefit all living organisms. Accordingly, the two important bodily processes that help human beings achieve a disease-free status, immune and homeostatic surveillance, can be positively regulated by a number of common natural products through the pathways depicted in Figure 1. Since accessible and published research is limited, the option of an in-depth delineation of more pathways or network systems possibly involved is currently unavailable. However, the study of other key processes under the influence of these and other products found in nature will undoubtedly reveal novel and less harmful therapeutic approaches.

**Competing Interests:** None to declare

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