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Appraisal the Importance of Dehydroepiandrosterone, Metabolites, and Genus Aspergillus in Cancer Research

Raghda Mahmood Abdulghafoor Al-ani*

Department of Chemistry, Institute of Natural Science, Sakarya University, Turkey

*raghda.alani996@gmail.com

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Abstract

Steroids are natural compounds found in animals, plants, fungi, and some bacteria. Microbial transformation plays a critical role in the biotransformation of steroids, enabling the production of compounds with high regional and spatial selectivity. Cancer remains one of the most significant scientific challenges, causing millions of deaths each year. Consequently, major research efforts are focused on discovering new therapies, particularly due to the emergence of certain fungi that exhibit anticancer properties, which could lead to innovative treatments. Metabolites, which are intermediate products of biochemical processes in living organisms, are essential for clinical diagnosis. Therefore, accurate detection of their concentrations is crucial.

In this work, I will describe an experiment published at the 1st International Karatekin Science and Technology Congress, held from September 1-3, 2022 in Çankırı, Turkey. The aim is to clarify the inputs, outputs, and processes to enhance the understanding of the key concepts discussed here. The experiment focused on incubating dehydroepiandrosterone (DHEA) with Aspergillus glaucus, which primarily resulted in the production of several hydroxylated metabolites. Discussing this experiment as one of the experiments that produces metabolites as a result of the biotransformation of steroids may have a major role in the development of promising treatments for cancer.

Keywords: Biotransformation, Steroids, Metabolism, Aspergillus species, Anti-cancer agents.

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Introduction

Biotransformation means the alteration of chemical molecules in a biological system and the produced metabolites may reach higher concentrations in the system than their parent compounds. Living cells such as bacteria, filamentous fungi, animals, plants, algae, yeast, and actinomycetes have been used as such biological systems [1].

The most effective and common application of biotransformation in manufacturing various biologically active compounds is the microbial transformation of steroids [2].

Steroids are compounds with similar structures that can be found in both animals and plants. They include cholesterol, vitamin D, bile acids, hormones produced by the adrenal cortex, and sex hormones.

Historically, the term "sterol" referred specifically to crystalline alcohols and is derived from the Greek word "stereos," which means solid.

Steroids have a molecular structure made up of four fused rings and play various roles in the body, making them important in biology and chemistry [3].

The basic structure of all steroids is identical: cyclopentanoperhydrophenanthrene, composed of four fused rings (Nes, 2011).

In the 18th century, the first therapeutic use of steroids was established by the English physician William Withering, who treated edema using digitalis, a compound derived from the leaves of the foxglove plant. Research on steroids progressed in the early 19th century with studies focused on unsaponifiable substances, particularly cholesterol, animal fats, gallstones, and bile acids. Cholesterol and some bile acids were isolated with a reasonable degree of purity, leading to the discovery of significant properties related to their structure [4].

Biotransformation in the current integrated drug discovery landscape offers opportunities to utilize insights from early-stage metabolic studies before selecting the final candidate for development. Research has consistently highlighted the significance of biotransformation as a crucial field of study, particularly in the conversion of natural bioactive compounds. [5].

Microorganisms are capable of performing complex reactions that are often economically unfeasible, such as chemical synthesis, due to their remarkable regioselectivity, chemo selectivity, photo reactivity, and reversibility. Many specific microbial transformations have been successfully integrated into steroid drug formulations and key mediators. This application of microorganisms in steroid biotransformation has garnered significant attention within the steroid chemistry community. Well-documented steroid transformations, including hydroxylation, dehydrogenation, redox reactions, and Baeyer-Villiger oxidation, have been identified in various microorganisms. Biotransformation methods are generally superior to traditional chemical synthesis, particularly when it comes to the challenge of attaching an oxygen atom to an inactive carbon atom in the steroid structure. As a result, these developments have enabled the creation of methods that yield high quantities of functional steroid compounds widely used in commercial production, such as corticosteroids [6].

Metabolomics are essential for the early detection and diagnosis of cancer, as well as for the assess of medical interventions and cancer treatments. A key aspect of cancer metabolism is the heightened dependence on aerobic glycolysis. This phenomenon has led to significant advancements in analytical techniques and statistical methods within metabolomics, allowing for a more in-depth exploration of cancer metabolism [7]. In the study published in Multidisciplinary Digital Publishing Institute (MDPI), the researchers highlighted the importance of marine natural products as major sources of bioactive molecules that have been shown to modulate a variety of biological functions, including as antioxidant, antimicrobial, and anticancer properties [8]. Scientists and researchers are trying to search nature for future drugs. The intriguing world of endophytic fungi is one potential area of research because fungi have been shown to make a variety of bioactive molecules with a wide range of biological effects. It could be a source of bioactive chemicals because some of it have antioxidant and anticancer capabilities [9].

In the study published in Frontiers in Oncology [10]. Researchers show that the main factors that influence tumor metabolic patterns are the activation of oncogenes genes and the inactivation of tumor suppressor genes. These changes lead to metabolic rewiring. In addition,

tumor metabolism can vary greatly depending on the cancer-causing changes present in different tumors.

DHEA (Dehydroepiandrosterone)

Dehydroepiandrosterone (DHEA) is a hormone that occurs naturally in the adrenal glands, gonads, and mental levels in every organ decrease as one ages [11].

This hormone is important in pharmacology, and its biological activities can vary based on hydroxylation at different positions. For instance, hydroxylation at the 9α and 16α positions is crucial for the biological functions of glucocorticoids like dexamethasone. Similarly, hydroxylation at the 11α position is vital for the anti-inflammatory effects of prednisolone [12]. It is essential to note that numerous earlier studies on the biotransformation of DHEA analogs discovered a diverse array of metabolites [13].

The genus Aspergillus

Fungi are widely used in research on microbial steroid conversion. Their diverse set of multifunctional enzymes can convert a large number of different types of steroids [14].

Fungi are a rich source of biologically active compounds with therapeutic potential. The genus Aspergillus is particularly noteworthy in biological research due to its capacity to produce a wide range of secondary metabolites. Many of these compounds demonstrate significant biological activities, including antibiotic and anticancer properties. Aspergillus species produce various compounds, such as alkaloids and butenolides, which are known for their anticancer activity [15].

Aspergillus glaucus is a resilient xerophilic fungus capable of thriving in various environments due to its physiological adaptations. This fungus may represent a mild pathogenic risk to humans [16].

Material and Methods

In previous biotransformation experiment towards DHEA-analog steroids aimed at obtaining new metabolites, they prepared a fungal growth medium by mixing 200 g of glucose, 5 g of peptone, 3 g of malt extract, and 3 g of yeast extract in one liter of distilled water. This mixture

was evenly distributed into ten 250 ml conical flasks and sterilized in a pressure vessel at 121 °C for 20 minutes.

After sterilization, aspergillus fungi were inoculated into each flask. The flasks were then incubated for three days at 25 °C while shaking at 150 rpm. Following the incubation period, 1 g of substrate dissolved in 10 ml of dimethyl formaldehyde was added aseptically to each flask. All flasks underwent the same conditions for an additional five days.

At the end of the incubation, the fungi were separated from the broth using vacuum filtration. For further analysis, chromatography was performed on silica gel using concentrations of ethyl acetate in n-hexane as a solvent. The outcomes from the incubation and column chromatography were evaluated using 0.2 mm TLC plates, with a solvent mixture of ethyl acetate and n-hexane in a 1:1 (v/v) ratio. For chromatographic development, the TLC plates were immersed in a reagent mixture of anisaldehyde and H2SO4 and then heated at 120 °C for 3 minutes.

Infrared (IR) spectra were recorded, and 1H NMR spectra were acquired in chloroform solvent $CDCl_3$ at 300 MHz in addition to, 13C NMR spectra.

Results and Discussion

The outcomes derived from the incubation DHEA (1) (1 g) (in 10 mL of Dimethylformamide DMF as a co-solvent) with A. glaucus MRC 200914 resulted in the generation of a certain amount of starting material (122 mg) along with two metabolites: 3β,11α-dihydroxyandrost-5-en-17-one (2) and 3β,7α-dihydroxyandrost-5-en-17-one (3). This is illustrated in Fig. 1.

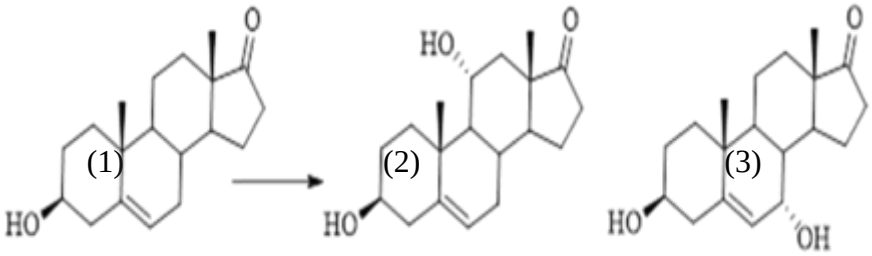

Figure 1: Biotransformation of the substrate by A. wentii MRC 200316 [17].

The result of elution with 70% ethyl acetate in n-hexane led to the production of 3β,11α-dihydroxyandrost-5-ene-17-one (compound 8) in an amount of 338 mg, which corresponds to a yield of 32%.

The acetylation using pure ethyl acetate resulted in the production of 3β,7α-hydroxyandrost-5-en-17-one (compound 9) in an amount of 317 mg, at a concentration of 30%.

The metabolites obtained from the experiment are considered to be metabolites of the biotransformation process of DHEA and have been the subject of extensive research in drug development and cancer research and has been the subject of further clinical trials.

DHEA and its metabolites affect estrogen receptors α or β, so evaluating the role of DHEA and its metabolites in activating estrogen receptors is essential to understanding the biological events of estrogen-mediated gene regulation in both normal and diseased tissues [18]. The differences in the effects of DHEA on cells are because steroids may be metabolized differently in different types of cells.

The Biological Significance of Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone is the most abundant steroid hormone found in human blood plasma. Sterol hormone DHEA is obtained from the mitochondria in the cells of the gonads and adrenal cortex. It has both preventive and therapeutic effects in treating major age-related diseases, including cancer, atherosclerosis, diabetes, and obesity. Additionally, DHEA helps to counteract the harmful effects of excessive cortisol exposure. Research has shown that low levels of DHEA are associated with an increased risk of death from all causes [19].

Some studies have shown that DHEA and DHEA biotransformation are associated with increased life expectancy and decreased life expectancy with age. Several studies have reported that serum DHEA levels decline almost linearly as people age, although there is significant inter-individual variability [20].

Anti-cancer agents from Aspergillus species

Dehydroepiandrosterone is one of the most abundant steroids in human blood. It is considered a substrate that can be transformed using many types of microorganisms. It can also perform various biological reactions, this result in a metabolism with beneficial biological activities and

It is characterized by being many times more active than DHEA especially with regard to the immune protection and immune regulation properties [21].

Several fungi have been used as a source of anticancer agents, and among fungi, species belonging to the genus Aspergillus have received increasing attention, because these fungal species have the ability to produce several secondary metabolic products with anticancer properties against a variety of cancer cells [22].

Fungi play a crucial role in drug discovery due to their diverse medicinal properties, particularly their anticancer and antioxidant activities. Bioactive natural products derived from marine fungi frequently demonstrate anticancer effects, offering new therapeutic options for the treatment of different types of cancer. Furthermore, fungal extracts have the potential to exhibit both antibacterial and anticancer properties through various mechanisms [9]

Various Aspergillus species produce a variety of active secondary metabolites, such as butanolides, alkaloids, terpenoids, and anthraquinone derivatives, all of which are of great importance in the pharmaceutical and commercial industries. Metabolites produced by different Aspergillus species have shown different biological activities, such as anti-inflammatory, anti-cancer, antibacterial, and antiviral activities [23].

Aspergillus species have garnered research interest to focus on novel anticancer agents. Their unique metabolic capabilities allow for the synthesis of a diverse array of biologically active compounds, which have proven to be highly effective against various types of cancer. The secondary metabolites of Aspergillus species, including terpenes, alkaloids, and polyketides, have demonstrated cytotoxic activity against specific cancer cell lines, such as those associated with colorectal cancer [24].

The Role of Metabolism in Cancer

Cancer cells are known for their rapid proliferation and their ability to constantly modify their metabolism to support tumor growth and enhance their energy supply.

These metabolic changes involve several pathways, including altered glycolysis, imbalanced lipid synthesis, excessive glutamine utilization, a shift toward the pentose phosphate pathway,

and mitochondrial dysfunction. Together, these changes are referred to as metabolic reprogramming.

This research has demonstrated that metabolic reprogramming in cancer cells is a hallmark of cancer and plays a significant role in drug resistance [10].

Conclusion

Biotransformation of steroid compounds is a simple way to obtain hydroxy derivatives at inactive positions. Although microbial strains capable of hydroxylation at any steroid position are known, a new organism that can perform the desired transformations still needs to be searched for.

Biotransformation of fungal steroids is an important process for creating novel steroid derivatives with potential pharmacological activities, owing to their high regioselectivity and stereoselectivity. There is a close relationship between the structure of the compound of steroids and its biological activity, so it has become important to work on developing effective methods to create active pharmaceutical ingredients, key intermediates and new derivatives, and biotransformation are good substitute to chemical synthesis in getting steroid derivatives

Fungi have emerged as a promising source of bioactive organic compounds with antioxidant and anticancer properties. Some Aspergillus species have shown the ability to generate biochemicals with high antioxidant resistance, as well as the ability to produce antioxidants with anticancer effects. A great deal of effort has been devoted to the analysis of natural compounds, especially those derived from fungi.

Fungi have emerged as a rich source of bioactive compounds with therapeutic potential. The genus Aspergillus occupies a special place in bioprospecting endeavors. Aspergillus species have been recognized for their ability to produce a myriad of secondary metabolites, many of which exhibit potent biological activities. These metabolites range from antibiotics and immunosuppressant's to agents with anticancer properties. Researchers should continue to conduct studies that define the role of receptors in cancer and elucidate the mechanisms that could lead to promising cancer treatments.

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