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REVIEW PAPER

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Cytotoxic and anti-cancer activity of the *Cistus* species of herbal plants

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ABSTRACT

Aim. The aim of this paper is to provide an overview of the cytotoxic and anti-cancer properties of the major species of the genus *Cistus*.

Materials and methods. Thirty four papers that discuss the medicinal history and current research of *Cistus* species as phytotherapeutics were used for this discussion.

Literature analysis.The growing popularity of the *Cistus* species of herbs is mainly due to its anti-inflammatory, antimicrobial, antifungal and antioxidant properties. The results of in vitro studies indicate that the presence of pear extract significantly affects leukemia, leukemia, breast, colon, ovarian, pancreatic, and melanoma carcinomas. The significant growth inhibition of these cells, underlines its valuable anti-tumor properties and allows for the possibility of use as a therapeutic aid.

Keywords. anti-tumor activity, *Cistus species*, cytotoxic activity, phytotherapeutics

Introduction

Herbs are a natural source of compounds that demonstrate bioactivity in humans.[1,2] *Cistus* species *(Cistaceae)* are of particular interest in the area of herbal plants because of the valuable aspects of pharmacological and antioxidant activity.[3-6]

The Cistus species of the family *Cistaceacea* are perennial shrubs naturally occurring in the Mediterranean, Europe and western Africa, and Asia.[7,8,9] *Cistus species* have been used since antiquity in Mediterranean cultures for their medicinal properties. Scientific literature confirms their valuable phytotherapeutic properties as anti-inflammatory, antibacterial, antifungal, antiviral, anti-allergic, antimicrobial, and analgesic agents.[10-18] Their biological activity is mainly due to antioxidant polyphenolic compounds that are present which are considered as potential therapeutic agents in a wide range of diseases such as hypertension, diabetes, and Alzheimer's disease among others.[4,19-21] Representative *Cistus species* incanus and creticus are shown in Figures 1 and 2.

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Figure 1. Herb Cistus incanus 22

The absence of antioxidant compounds such as phytotherapeutics in the human diet which provide the ability to deactivate free radicals can lead to dysfunction in the body, causing many diseases such as cancer, premature aging, and heart attacks.[23-26]

The aim of this paper is to characterize the cytotoxic and anti-cancer properties of the major species of the genus *Cistus*, with particular reference to the *Cistus creticus* subspecies *cretenicus L., Cistus incanus L. and Cistus monspeliensis L., C. creticus ssp. Creticus, Cistus libanotis, C. villosus and C. monspeliensis, C. ladanifer* and *C. populifolius, C. salviifolius* and their role as phytotherapeutic compounds.

Dimas et al. isolated 9 labdane diterpenes from the *Cistus creticus* subspecies *cretenicus (L.)* plant and ladano resin (extracted to the surface of leaves and stems of the plant). In vitro studies of the effects of the above diterpenes on 14 lines of human leukemic cells (CCRF-CEM, MOLT-3 H33AJ-JA13, HUT78, H9 (T cell lines) KM3, NAMALWA, DAUDI SDK, JIYOYE, CCRF- HL 60 (promyelocyte cell line) K562 (proerythrocytes) and U937 (monocytes) indicated cytotoxic activity. (13E) -labd-13-ene-8 alpha 15-diol showed cytotoxic activity against 13 cell lines tested, while (13E) -labd-7,13-dienol showed activity only against the HL60 cell line.[28]

In studies by Vitali et al., a significant effect of polyphenol compounds present in *Cistus incanus L.* and *Cistus monspeliensis L.* was indicated. These polyphenolic compounds showed cytotoxic effects on the human prostate cells (PZ-HPV-7 and PNT1A) and the lung fibroblast cell line (V79-4) in a reduction of cell viability.[29] These substances present in the extracts of *Cistus incanus L.* and *Cistus monspeliensis L.* may be beneficial in the treatment of benign prostatic hypertrophy (BPH).[29]

Studies of *C. ladanifer* and *C. populifolius* subspecies analyzed in vitro have confirmed their valuable antioxidant properties as well as cytotoxicity to human tumor cells. *C. populifolius* and *C. ladanifer* extract showed the ability to inhibit the proliferation of M220 pancreatic cancer cells and the breast cancer cells MCF7 / HER2 and JIMT-1.[30] The leaves of these plants are a source of water-soluble polyphenol extracts enriched with ellagitannins with antioxidant activity, and their cytotoxic effect on neoplastic cells deserves further attention.

Figure 2. Herb Cistus creticus L. 27

Another subspecies of *C. creticus ssp.* has also been characterized by cytotoxic activity against tumor cells. Ethanol extracts of *C. creticus ssp*. present in culture inhibit the development of cervical cancer cell lines (HeLa), breast cancer (MDA-MB-453) and melanoma (FemX). It was determined that the agents responsible for this inhibition are present in the diterpenes type labdan purified extract.[31]

The phytochemical studies of extracts from *Cistus libanotis, C. villosus* and *C. monspeliensis,* highlight their antiproliferative activity. When introduced to the culture, extracts from these species show great antiproliferative activity against human melanoma cell lines (A-375) than human breast cancer cells (MCF-7).[32]

El Euch et al. attempted to evaluate the difference in cytotoxicity between leaf extracts and flower buds (FB) of the *Cistus salviifolius* strain. They determined that the FB extract exhibited higher cytotoxic activity against OVCAR and MCF-7 ovarian cancer cells compared to leaves that were inactive at a concentration of 50 mg/L. The extract location was found to significantly affect the composition and biological activity of C. salviifolius.[33]

Studies have reported that extracts from *Cistus incanus L.* and pomegranate (*Punica granatum L.)* which are rich in polyphenolic compounds showed significant antioxidant activity. The addition of *Cistus* to breast cancer cell lines (MCF-7) and colon (LOVO) and addition of pomegranate extracts to both drug-sensitive and drug-resistant (doxorubicin-resistant) tumor cells resulted in apoptosis.[34] A higher proapoptotic effect of extract was observed in drug-sensitive cell lines than in drug-resistant cells. The authors suggest that the extracted could be used by persons exposed to oxidative stress.[34]

Conclusion

The results of scientific research literature presented in this paper characterize *Cistus* species as a medicinal plant with biological activity with emphasis on their antitumor properties. This is due to the presence of polyphenolic compounds such as labdan type diterpens and ellagitannins that may be considered potential therapeutic agents in the treatment of many cancers. However, the use of *Cistus* extracts as a complement to the treatment of human cancers requires further research to thoroughly understand the effects and interactions with recommended medicines.

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