REVIEW

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2024.2024-91
Cyprus J Med Sci 2025;10(2):94-110

A Review of the Anti-Breast Cancer Activity of Non-Endemic Medicinal Plants in Cyprus

Gülseren Çırban[1], Mustafa Çavuşoğlu[2], Shideh Roshani[3], Göksu Oduncuoğlu[4]

[1]Department of Pharmacognosy, Girne American University Faculty of Pharmacy, Kyrenia, Cyprus
[2]Department of Medical Biology and Genetics, Girne American University Faculty of Medicine, Kyrenia, Cyprus
[3]Department of Pharmacology, University of Kyrenia Faculty of Medicine, Kyrenia, Cyprus
[4]Department of Pharmacognosy, Bahçeşehir Cyprus University Faculty of Pharmacy, Nicosia, Cyprus

Abstract

Breast cancer is a widespread health concern that begins in the breast cells and leads to uncontrollable growth of these cells. This disease has a physiological basis as it is associated with physical abnormalities arising from defective genes in breast cancer genes, such as *BRCA1* and *BRCA2*, and non-functional tumor suppressor genes, such as *p53*, which leads to the transformation of tissues into malignant and metastatic forms. Despite the progressive modern methods of cancer treatment with the help of chemotherapy, radiation therapy, surgery, endocrine therapy, and immunotherapy, most treatments result in furious side effects that disturb patients' quality of life. As a result, researchers and scientists have shifted their focus to medicinal plants and their secondary metabolites as potential treatments for breast cancer. This research aims to review the medicinal plants used in Cyprus for lethal diseases, such as breast cancer, from various species of herbs, as well as the knowledge generated from traditional practices and recent studies. This study also describes the geographical origins, status, and potential applications of these plants in breast cancer treatment, providing valuable insights into their therapeutic value.

Keywords: Breast cancer, bioactive compounds, complementary therapy, medicinal plants

INTRODUCTION

Globally, breast cancer has emerged as a significant cancer, with >2.3 million diagnoses and 685,000 deaths reported in 2020 alone.[1] Equivalent to these results, based only on Cyprus, as seen in studies conducted between 2004 and 2017, the rate of breast cancer per 100,000 people, especially in the elderly population, increased from 135.3 to 153.2.[2] Breast cancer is a disease that affects most people and has a significant impact worldwide. It is caused by the mutation of breast cells and their uncontrolled growth and spread.[3] Physiologically, breast cancer occurs when specific genes of breast cells become defective, resulting in uncontrollable growth of cell clusters.[4] Changes in genes like *BRCA1* and *BRCA2*, which repair DNA and direct cell division, can accompany this process.[5] Thereby, the loss of function in tumor suppressor genes such as *p53* and disruption of cell cycle regulators also leads to malignant transformation of cells.[6] Furthermore, new blood vessel formation (angiogenesis) sustains tumor growth potentials for metastasis, which is the spread of cancer cells to other regions of the body.[7] Modern medicine's oncological developments in breast cancer treatment are driving efforts to alter the disease's trajectory through combined or simple treatment methods.[8] These treatment methods are associated with cell cycle regulation and apoptosis stimulation, and they include the stimulation of the supporting immune system stimulation.[9,10] Comprehensive modern medical applications carried

To cite this article: Çırban G, Çavuşoğlu M, Roshani S, Oduncuoğlu G. A review of the anti-breast cancer activity of non-endemic medicinal plants in Cyprus. Cyprus J Med Sci. 2025;10(2):94-110

ORCID IDs of the authors: G.Ç. 0009-0007-4183-0632; M.Ç. 0000-0002-8221-6299; S.R. 0009-0008-0594-0364; G.O. 0000-0003-2853-0938.

Corresponding author: Göksu Oduncuoğlu
E-mail: goksu.oduncuoglu@baucyprus.edu.tr
ORCID ID: orcid.org/0000-0003-2853-0938

Received: 10.09.2024
Accepted: 24.12.2024
Epub: 15.04.2025
Publication Date: 18.04.2025

out to examine these effects in oncology include treatment methods such as chemotherapy, radiotherapy, surgical intervention, hormone therapy, and immunotherapy, and the application to be used is decided according to the course of treatment and the stage and type of breast cancer.[11,12] Despite the significant advancements in medicine, these treatment methods still cause side effects, such as nausea, vomiting, decreased immunity, and fatigue, which can significantly lower the patient's quality of life.[13] Therefore, researchers are focusing on secondary metabolites found in plants to enhance patients' overall quality of life and prevent damage to healthy tissues that conventional methods may cause.[14] Secondary metabolites are organic compounds produced by medicinal plants but are not directly involved in their growth, development, or reproduction.[15] When used in cancer cells, secondary metabolites exhibit anticancer activity. These substances can prevent cancer cell overgrowth, trigger apoptosis, or inhibit cell proliferation.[16] Therefore, medicinal plants and their secondary metabolites can be considered a safer treatment strategy for breast cancer.[17] In the field of cancer treatment using medicinal plants in Cyprus, this approach has an intriguing aspect due to the rich herbal biodiversity and herbal medicine knowledge provided by the Mediterranean climate.[18]

The purpose of this narrative review is to gather research on how local medicinal herbs in Cyprus can protect against breast cancer. The local populace in Cyprus places historical and contemporary value on the plants chosen for this study. This review marks a significant milestone as it delves into the anti-cancer capabilities of medicinal plants that grow wild in Cyprus. The results are summarized in Table 1. For this investigation, we identified pertinent plants by consulting the most recent sources. The medicinal plants reviewed are *Aloe Vera, Artemisia Annua, Calendula Officinalis, Catharanthus Roseus, Ceratonia Siliqua, Cicer Arietinum, Citrullus Colocynthis, Ficus Carica, Glycyrrhiza Glabra, Hordeum Vulgare, Myrtus Communis, Nigella Sativa, Olea Europaea, Rosmarinus Officinalis,* and *Silybum Marianum*. According to the evaluated sources, some of these plants are indigenous (IN) to Cyprus, while others are considered casual (CA). While plants classified as casual have not yet established a stable habitat and may not stay there permanently, those classified as IN naturally thrive and adapt to certain geographic locations or ecosystems.[19]

Method

A narrative overview of the literature was conducted using Google Scholar, PubMed, and Web of Science. The database was searched using relevant keywords, including MCF-7 cells, anticancer properties, medicinal plants, breast cancer, MDA-MB-231, and MDA-MB-436. To obtain recent findings, scientific articles published in 2018 and later were selected. The most common plants that have traditional uses in Cyprus and are easily accessible by local people were selected and included in this study. This study summarizes the anti-breast cancer activity of plants that are globally accessible, excluding endemic species found only in Cyprus. By focusing on widely distributed plants, this study highlights those with broader availability. The "Flora of Cyprus" website has also been utilized to offer details regarding the status and distribution of medicinal plants in Cyprus. According to this dynamic checklist, the island is divided into eight phytogeographic regions, which are listed from division 1 to division 8, as shown in Figure 1. The different ecological characteristics define each region. Division 1 is the Akamas Peninsula; division 2 is the Troodos Range; division 3 is the South Area around Limassol; division 4 is the Larnaca Area; division 5 is the East part of the Central Plain; division 6 is the West part of the central plain; division 7 is the North Slopes and Peaks of Pentadactylos; and division 8 is the Karpasia Peninsula.[20]

Medicinal Plants with Antibacterial Activity Against Breast Cancer

Aloe vera

Aloe vera, also known as *Aloe barbadensis Mill*., belongs to the Asphodelaceae family. It is named after the Arabic word "Alloeh," referring to "shining bitter substance," and the Latin word "vera," which refers to "true." *Aloe vera* was esteemed as "the plant of immortality" by the ancient Egyptians. It boasts triangular, succulent leaves with jagged edges, golden tubular blooms, and fruit carrying numerous seeds.[21,22] Traditionally, *Aloe vera* resin has been used to treat ailments like diabetes, obesity, and various types of infections.[23] Its historical uses span constipation relief, wound healing, and notably, the combat against tumors, which is also acknowledged in Chinese materia medica.[22,23] *Aloe vera*, which has many uses in tradition, is used daily by local people in Cyprus, mostly by applying the liquid inside the leaf to heal burns.[24] In addition, this resilient succulent appears to be CA in the island's botanical realm. Divisions 1, 4, and 6 indicate specific geographically defined regions where the resilient succulent thrives (Figure 2).[25] Studies investigating the anti-cancer activity of *Aloe vera* compounds against breast cancer cell lines. Aloe-emodin and ALE-α-Fe2O3NPs obtained from *Aloe vera* leaf extract appear to be effective anticancer agents against MCF-7 cells by inducing apoptosis via mitochondrial and endoplasmic reticulum pathways while inhibiting metastatic oxidative stress by itself.[21,26] Furthermore, studies have shown that aloe-emodin, 7-hydroxy-2,5 dimethylchromene, and betasitosterol compounds have a higher binding affinity toward estrogen alpha receptor when compared to tamoxifen.[27] Moreover, researchers found barbaloin, aloe-emodin, aloesin, and aloin to be cytotoxic compounds active against MCF-7 and MDA-MB-231 breast cancer cell lines. They act by inhibiting cell proliferation and inducing cell death.[28] In addition, 7-demethylsiderin, which was extracted from *Aloe vera* resin, had the strongest cytotoxic effect on MDA-MB-231 breast cancer cells.[23]

Artemisia annua

Botanists often refer to *Artemisia annua*, also known as sweet Wormwood, as the largest species in the genus *Artemisia annua*, belonging to the Asteraceae family. The name of this life form clearly indicates that it is an annual herbaceous plant, which means it grows annually. It follows the annual breeding process. *Artemisia annua* has versatile anatomical and morphological attributes. Its stems appear either bare or adorned with T-shaped hairs, while the upper layers house glandular cells that are rich in essential oil. The tiny, spherical form and yellow-green coloration of the flower heads, which are arranged in raceme-like inflorescences, distinguish them. Although the leaves emit a pleasant aroma, the flowers have no odor.[29] Historically, people have used *Artemisia annua* in various forms, like tea or pressed juice, to treat malaria, fever, and neurological disorders.[29-32] The *Artemisia annua* is commonly consumed among the people of Cyprus, often through the consumption of infusion tea derived from its flowers and young leaves. It is known for its ability to suppress cough and regulate menstruation. Furthermore, studies have shown that its flowers possess additional pharmacological properties, such as aphrodisiac, antipyretic, and antispasmodic effects.[24]

Table 1. Summary of the anti-breast cancer activities of medicinal plant extracts and their isolated bioactive compounds

Plant	Bioactive compounds and their mechanism of action	Cell lines	Divisions	References
Aloe vera	Compounds from aloe vera, including aloe-emodin, ALE-α-Fe_2O_3NPs, barbaloin, aloin, and 7-demethylsiderin, exert anticancer effects by promoting apoptosis and suppressing cell growth in breast cancer cells. The chemicals induce apoptosis through mitochondrial and endoplasmic reticulum stress pathways, mitigate metastatic oxidative stress, and interact with estrogen receptors. 7-demethylsiderin specifically targets carbonic anhydrase II.	MCF-7, DA-MB-231	1, 4, 6	21,23,26-28
Artemisia annua (Wormwood)	It exhibits potent anticancer capabilities via its bioactive components, promoting apoptosis and cell cycle arrest in neoplastic cells. Compounds such as chrysosplenol D, cacticin, and dihydroartemisinin are responsible for these effects. The plant's chemicals promote apoptosis, induce cell cycle arrest at both G1 and G2/M stages, and suppress tumor growth by targeting proteins such as CD44, Oct 3/4, and MMP-9. Dihydroartemisinin augments the efficacy of chemotherapy (docetaxel), whereas artesunate causes both ROS-dependent and ROS-independent cell cycle arrest.	MDA-MB-231, MCF-7	6	9,16,24,25,29-32
Calendula officinalis (Marigold)	The extracts exhibit specific cytotoxicity toward cancer cells while preserving healthy cells. The plant's constituents, including saponins, tannins, flavonoids, and lutein, promote apoptosis, induce cell cycle arrest at the G0/G1 phase, and impede cancer cell viability. Moreover, tin nanoparticles generated from its aqueous extract exhibit antioxidant capabilities and cytotoxicity toward breast cancer cells, notably in a manner that is dependent on both time and dosage.	MCF-7, MDA-MB-231, MCF10A	2, 3	13,24,25,28,33-36
Catharanthus roseus (Madagascar periwinkle)	It synthesizes anticancer agents such as vinblastine, vincristine, and dimeric indole alkaloids. These chemicals are cytotoxic and impede cancer cell proliferation. These chemicals promote apoptosis and decrease HER-2 expression in breast cancer cells. Incensole acetate derived from the plant's essential oil has a binding affinity for estrogen receptors (ER-positive), comparable to those of fulvestrant and bazedoxifene.	MDA-MB-231 and HER-2-positive breast cancer cell lines	1	24,25,37-41
Ceratonia siliqua (Carob)	It exhibits anticancer characteristics, primarily due to its elevated levels of polyphenols, including myricetin, naringenin, and kaempferol, which promote apoptosis and suppress growth in breast cancer cells. Diethyl ether and ethyl acetate extracts from Carob fruit, which are abundant in polyphenols, specifically impede cancer cell proliferation and trigger apoptosis in MCF-7 cells. Ethanolic extracts exhibited antiproliferative effects on MCF-7, MDA-MB-231, and MDA-MB-436 cells, with MCF-7 exhibiting the greatest sensitivity. Methanolic leaf extracts rich in gallic acid, chlorogenic acid, and flavonoids elicit cytotoxicity and elevate sub-G1 cell populations in a concentration-dependent manner.	MCF-7, MDA-MB-231, MDA-MB-436	1, 2, 3, 4, 6, 7, 8	1,24,25,42-45
Cicer arietinum (Chickpea)	It includes isoflavone, including biochanin A, genistein, formononetin, and trifolyrhizin, which demonstrate significant anticancer properties by suppressing cell growth, causing apoptosis, and influencing cell cycle progression. The mechanism of action of isoflavone derived from sprouted Chickpeas involves the inhibition of breast cancer cell proliferation through the induction of mitochondria-dependent apoptosis, cessation of cell adhesion, and modification of cell shape. These chemicals also diminish EGF-induced p44/42 MAPK signaling and stimulate the NF-κB pathway, which governs apoptosis and proliferation. Moreover, lectin and protease inhibitor concentrates impede cell division and promote apoptosis throughout the S and G2 phases of the cell cycle.	MDA-MB-231, SKBr3, and MCF-7	1, 2, 3	24,25,42,46-49
Citrullus colocynthis (Bitter apple)	It exhibits notable anticancer properties owing to its bioactive components, especially cucurbitacin glycoside, which triggers apoptosis and cell cycle arrest in breast cancer cells. Cucurbitacin glycoside from leaves interferes with proteolytic complexes crucial for G2/M cell cycle transition. The ethanololic extracts of seeds comprise ethylbenzene and tetrachloroethylene, which are toxic to MDA-MB-231 cells. The ethanol and methanolic extracts of leaves promote apoptosis via caspase-3 activation and the modulation of pro-apoptotic genes. These extracts also modulate cholesterol and triglyceride levels, which are essential for the survival of breast cancer cells.	MCF-7, MDA-MB-231	1, 5, 7	15,24,25,42,50-59
Ficus carica (Fig)	It exhibits significant anticancer effects of flavonoids, tannins, alkaloids, polyphenols, and hydrolytic enzymes. These chemicals are present in Fig leaf and latex extracts and have anticancer properties in breast cancer studies. The mechanism of action involves flavonoids and tannins from Fig leaves, which cause apoptosis and suppress cell proliferation in MCF-7 cells. Figure 4. Latex, abundant in alkaloids and polyphenols, diminishes ERK2, CREB, and AKT2 levels, resulting in reduced tumor proliferation. Bergapten and psoralen cause S-phase cell cycle arrest, facilitate apoptosis, and diminish cell motility in MDA-MB-231 cells.	MCF-7, MDA-MB-231, MCF10A	1, 2, 3, 5	24,25,42,60-65
Glycyrrhiza glabra (Licorice)	The anticancer properties of glycyrrhizin are chiefly attributable to its constituent glycyrrhizin and its derivatives, which promote apoptosis, impede cell proliferation, and prevent metastasis. Glycyrrhizin and its derivatives activate caspases to promote apoptosis and block FAK/Rho signaling to prevent metastasis in MDA-MB-231 cells. Furthermore, glycyrrhizin elevates miR-200c and e-cadherin levels, thereby diminishing cancer cell invasiveness. Glycyrrhetinic acid modulates VEGFR2, triggers mitochondria-dependent apoptosis, and influences the p38 MAPK-AP1 pathway, thereby affecting tumor proliferation and metastasis. Root extract affects the viability of 4T1, MCF-7, and HER-2 cells by generating morphological alterations.	MDA-MB-231, BT549, 4T1, MCF-7, HER-2	3, 4, 5, 7	24,25,42,66-69,71-73

Table 1. continued

Plant	Bioactive compounds and their mechanism of action	Cell lines	Divisions	References
Hordeum vulgare (Barley)	Anticancer chemicals, including gramine and hordenine, that demonstrate substantial anticancer efficacy, especially against breast cancer cells. Bioactive constituents inhibit cancer cell proliferation and promote apoptosis. Gramine activates the adiponectin receptor 2 pathway, thereby reducing MDA-MB-231 and MCF-7 cell proliferation. Hordenine derived from germinated Barley seed initiates extrinsic apoptosis, whereas palmitic acid promotes apoptosis by activating caspase-3, Bax, and p53. Moreover, Barley bran polyphenols diminish the viability of breast cancer cells, whereas fermented Barley extract exhibits potential in inhibiting the progression of non-invasive breast cancer to an invasive form.	MDA-MB-231, MCF-7, EMT6/p, TNBC	2	11,24,25,42,48,74-76
Myrtus communis (Myrtle)	Essential oils and extracts exert anticancer effects, particularly by triggering apoptosis in breast cancer cells. Mode of action: the essential oil, which is abundant in alpha-pinene, 1,8-cineole, and linalool, exerts cytotoxic effects on breast cancer cells such as MCF-7. Significantly, 1,8-cineole specifically triggers apoptosis in cancerous cells while sparing healthy cells. β-ionone is a significant component of the essential oil, and it can prevent cancer growth both *in vitro* and *in vivo*. Myrtucommulone derived from the leaves augments the activity of caspase 3 and 9, resulting in PARP cleavage and apoptotic DNA fragmentation. Methanolic extracts exert significant cytotoxic effects on breast cancer cell lines.	MCF-7, MCF10A	All	24,25,42,67,77-81
Nigella sativa (Black cumin)	Essential components such as thymoquinone, thymol, and thymoquinone, which demonstrate significant anticancer properties, especially against breast cancer cells. Thymoquinone diminishes tumor growth, enhances p53 expression, and reduces BRCA1 and BRCA2 levels. It also impedes metastasis by downregulating CXCR4 expression. Nanosized emulsions and silver nanoparticles from *Nigella sativa* promote apoptosis in MCF-7 cells by modulating Bax, Bcl-2, and Cox-2. Thymoquinone, when administered with tamoxifen, amplifies apoptosis in both ER-positive and ER-negative breast cancer cells. Moreover, nanostructured lipid carriers infused with thymoquinone were effective against MDA-MB-231 and MCF-7 cell lines.	MCF-7, MDA-MB-231	2, 3, 7	24,25,42,63,82,83,85,86
Olea europaea (Olive tree)	The treatment includes bioactive substances, primarily oleuropein (OLE) and oleocanthal, which demonstrate considerable anticancer efficacy. OLE decreased the viability of MCF-7 cells in a dose- and time-dependent manner, promoting apoptosis and decreasing invasiveness. It accomplishes this by regulating HDAC4, suppressing ERK1/2 through estrogen signaling, and activating the NF-κB pathway. In conjunction with doxorubicin, OLE further diminishes NF-κB, Bcl-2, and survivin, thereby facilitating apoptosis in MDA-MB-231 cells. Oleocanthal treatment inhibits MCF-7 and MDA-MB-231 cell proliferation while sparing normal cells. Moreover, apigenin and hydroxytyrosol inhibit growth factor receptors, resulting in cell cycle arrest at the G2/M and G1/S phases in MCF-7 cells.	MCF-7, BT474, MDA-MB-231	1, 2, 3, 4, 7, 8	2,24,25,42,87-91
Rosmarinus officinalis (Rosemary)	Bioactive substances such as carnosic acid, rosmarinic acid, oleanolic acid, betulinic acid, and flavonoids, all of which have considerable anticancer effects. Rosemary essential oil and its constituents promote apoptosis in breast cancer cells, specifically MCF-7 and TNBC cells, such as MDA-MB-231 and MDA-MB-468. Carnosol and uric acid suppress NF-κB pathways, obstruct carcinogenesis, and impede Cox-2 production, which is essential for cancer growth. Rosmarinic acid modulates apoptosis-associated genes and is particularly potent against TNBC cells. Silver nanoparticles produced from Rosemary exert lethal effects on breast cancer cells, inhibiting disease development.	MCF-7, MDA-MB-231, and MDA-MB-468	1, 8	10,24,25,42,63,92-96
Silybum marianum (Milk thistle)	Contains silymarin and its active constituent silibinin, which exhibit significant anticancer properties, particularly against breast cancer. Silymarin causes cell cycle arrest and death in MDA-MB-468 and MCF-7 breast cancer cells by upregulating p53 and downregulating VEGF and matrix metalloproteinases. Silibinin exhibits a dose- and time-dependent effect on the inhibition of MCF-7 cell proliferation, demonstrating synergistic effects when administered alongside chemotherapeutic drugs, such as doxorubicin, carboplatin, and cisplatin. The encapsulation of silibinin in nanoparticles has demonstrated increased apoptotic efficacy.	MDA-MB-468, MCF-7	2, 3, 4, 5, 6, 8	12,24,25,100-102

ROS: Reactive oxygen species, PARP: Poly (ADP-ribose) polymerase, TNBC: Triple-negative breast cancer, VEGF: Vascular endothelial growth factor, ER: Estrogen receptor, HER-2: Human epidermal growth factor receptor-2.

In Cyprus, *Artemisia annua* is a notable species and is categorized as CA. As shown in Figure 3, this plant belongs to division 6, indicating its presence in a specific region of the island.[25] The extract from *Artemisia annua*, which is particularly enriched through acetonitrile maceration, contains flavonols such as chrysosplenol D and cacticin, which trigger apoptosis and cell cycle arrest, thereby eliminating MDA-MB-231 and MCF-7 breast cancer cells.[31,32] Moreover, polyphenols from the extracts of *Artemisia annua* exhibit a tendency to act as anti-cancer agents by notably killing CD44, Oct-3/4, catenin, and MMP-9 proteins, which are associated with radio resistance in MDA-MB-231 human breast cancer cells.[30] Coactive substances like syringaldehyde and quercetin from *Artemisia annua* have an inhibitory function, leading to the prevention of the migration of MDA-MB-231 cells toward endothelial cells.[29] Dihydroartemisinin, the main active metabolite of artemisinin from *Artemisia annua*, slows down cell division, induces apoptosis, and prevents tumor expansion in breast cancer cells. When administered in conjunction with dihydroartemisinin, docetaxel enhances the effectiveness of chemical therapy.[16] Artesunate, another derivative of

artemisinin, shows remarkable antitumor activity mainly via apoptosis and cell cycle arrest in both triple-negative breast cancer (TNBC) and HER-2-enriched cell lines.[9,16] These substances further suppress cancer cell growth by inducing reactive oxygen species (ROS)-dependent G2/M-phase cell cycle arrest and ROS-independent G1 phase cell cycle arrest.[9]

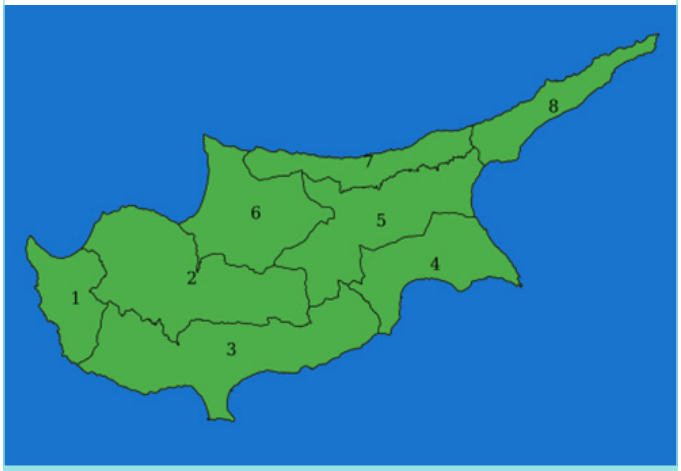

Figure 1. Eight phytogeographic regions in Cyprus from division 1 to division 8.[25]

Figure 2. *Aloe vera* (*Aloe barbadensis Mill.*) photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Aloe vera* in Cyprus. Areas marked in yellow indicate divisions where *Aloe vera* casually grows (CA).[25] Photographer: G. N. Hadjikyriakou.

Calendula officinalis

Calendula officinalis, commonly referred to as Marigold, is a botanical marvel celebrated for its multifaceted medicinal properties within the Asteraceae family.[33] Embraced in traditional medicine across diverse cultures, *Calendula officinalis* flowers and leaves are used to treat an array of ailments, including poorly healed wounds, bruises, rashes, burns, and gastrointestinal discomfort.[13,34,35] Notably, extracts from flowers, leaves, and roots exhibit promising antitumor effects both *in vitro* and *in vivo*, accentuating their potential in cancer management.[28,34] The local people of Cyprus have observed that this medicinal plant has a therapeutic effect by crushing its flowers, extracting the oil, and applying it to inflamed and injured areas. Additionally, brewing and drinking dried calendula flowers as tea can alleviate stomach disorders like stomach ulcers and gastritis.[24] Cyprus classifies *Calendula officinalis* as CA; it primarily thrives in divisions 2 and 3, which encompass specific regions (Figure 4) across the island. This medicinal plant appears to be a promising candidate in Cyprus, warranting further investigation for its potential role in combating breast cancer.[25] The MDA-MB-231 breast cancer and MCF10A normal cell lines were used to evaluate the activity of *Calendula officinalis* flowers extract. Notably, this extract demonstrated approximately 40% cancer cell survival while maintaining the viability of normal breast cells.[28,36] Examining the extract's chemical structure revealed the presence of numerous bioactive compounds like saponins, tannins, and flavonoids, which are believed to collectively contribute to its cytotoxicity. Additionally, the investigations revealed that a semi-purified *Calendula officinalis* flower extract induces apoptosis

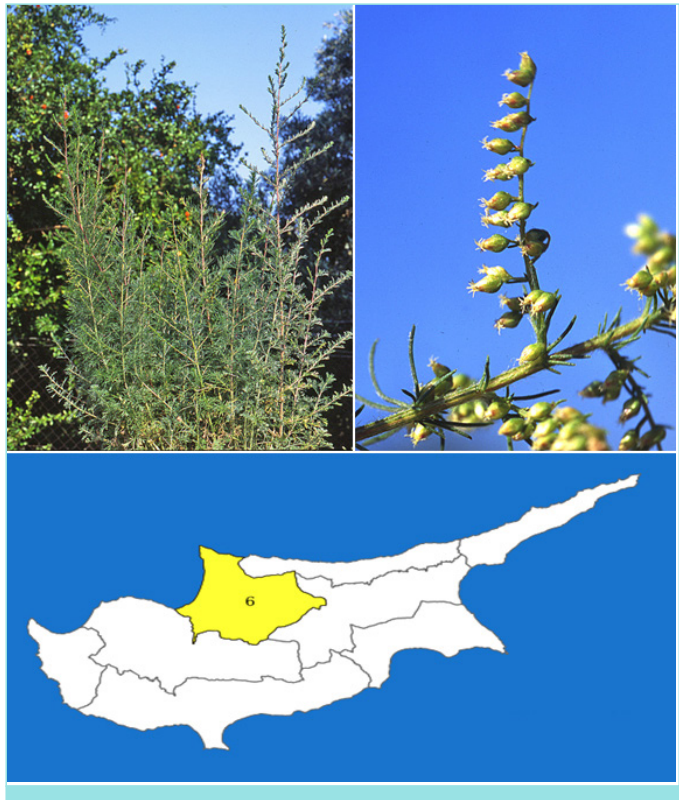

Figure 3. *Artemisia annua* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Artemisia annua* in Cyprus. The yellow area indicates the division where *Artemisia annua* grows casually (CA).[25] Photographer: G. N. Hadjikyriakou.

and cell cycle arrest, particularly in the case of the MCF-7 cell line.[28] Additionally, in a study conducted with ultrasonic-assisted extraction of dried flowers and leaves in methanol, it was observed that the cell lethality and selectivity of the flower extract were higher than those of the leaf extract.[34,36] Scientists have discovered that extracts of *Calendula officinalis* cause cell death in the G0/G1 phase and kill MCF-7 cells.[34] Another crucial discovery was that scientists used the aqueous extract of *Calendula officinalis* to produce "green-synthesized tin nanoparticles," which have demonstrated effective anti-breast cancer agents (inhibitory effects) for the MCF-7 cell line because of their antioxidant effects. These nanoparticles exhibited time- and dose-dependent cytotoxicity, suggesting their potential as adjuvant therapeutic chemotherapeutic agents.[35] The methanolic leaf extracts of *Calendula officinalis* selectively killed different types of breast cancer cells while having little effect on healthy cells.[33] Notably, lutein, a chemical isolated from *Calendula officinalis*, is more effective at killing TNBC cells than other types of cancer cells, suggesting its potential use as targeted therapy.[13]

Catharanthus roseus

Catharanthus roseus, also known as Madagascar periwinkle, is a rose-like plant belonging to the Apocynaceae family that is native to Madagascar. The flowering is more visible at the axillary, giving the plant a white-red bloom spectrum. Additionally, *Catharanthus roseus* is a highly adaptable plant, and its rapid spread and growth can support its growth in a variety of climates.[37] People not only value this plant for its decorative beauty, but also for its aromatic and medicinal qualities.[37,38] Therefore, the traditional method involves immersing the dry leaf or entire plant of *Catharanthus roseus* in boiling water and then consuming the resulting decoction to treat diabetes.[38] In addition, local people have been using liquid extracts of leaves or entire plants as long-term treatments for cancers such as breast, throat, lung, and esophageal cancers.[37,38] Local people have been using *Catharanthus roseus* orally for its hypoglycemic effect, which has been known for its cancer benefits for many years and has greatly contributed to the production of modern cancer drugs.[24] *Catharanthus roseus* occupies a notable place in the flora of Cyprus, characterized by its CA status. As a location, division 1 designates its occurrence in specific regions of Cyprus, providing insights into its distribution within the island (Figure 5).[25] Recently, medicinal plants, especially *Catharanthus roseus*, which is a great source of anticancer compounds, namely vinblastine and vincristine, have become very important tools in the fight against breast cancer.[37,38] Studies based on both animal and cellular models have extensively examined the effectiveness of *Catharanthus roseus*. A group of researchers wanted to make PLGA-based polymeric nanoparticles that were full of *Catharanthus roseus*. These particles can bind to HER-2 overexpression for the treatment of breast cancer. The results indicated that both PLGA-PEG *Catharanthus roseus* (PLGA-PEG CR) formulations have cytotoxic effects, with sustained release observed in PLGA-PEG CR G68 and downregulation of HER-2 expression induced by PLGA-PEG CR F68.[37] In another study, the effect of incense acetate (IA), a compound of *Catharanthus roseus* essential oil and its nanoemulsion, on breast cancer cells. The IA-based nanoformulation

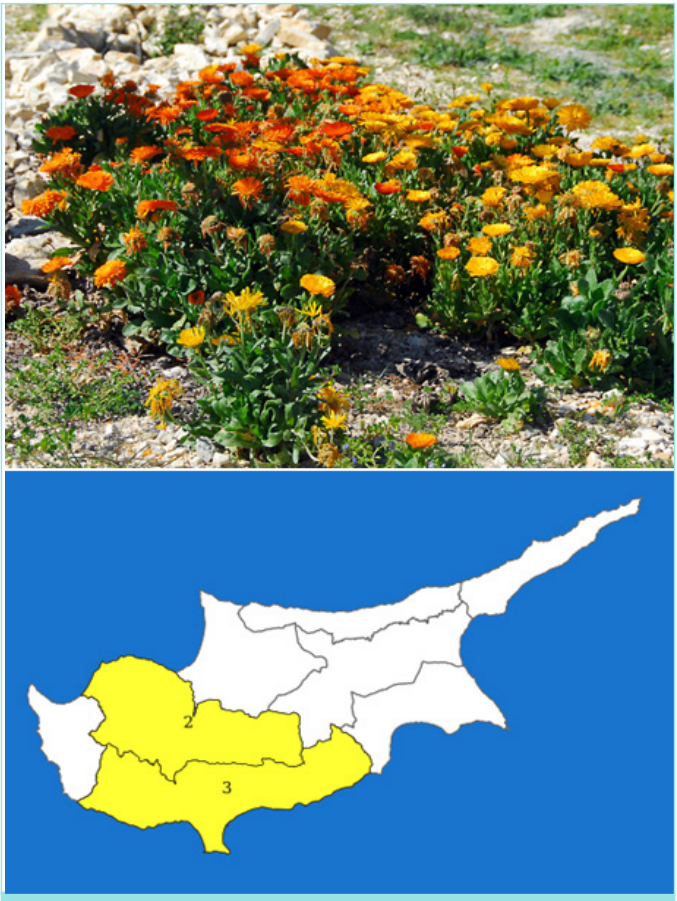

Figure 4. *Calendula officinalis* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Calendula officinalis* in Cyprus. Areas marked in yellow indicate divisions where *Calendula officinalis* grows casually (CA).[25] Photographer: G. N. Hadjikyriakou.

Figure 5. *Catharanthus roseus* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Catharanthus roseus* in Cyprus. The yellow area indicates the division where *Catharanthus roseus* grows casually (CA).[25] Photographer: Authors.

demonstrated cytotoxicity against breast cancer cell lines, with "*in vitro*" improvements that were promising and nearly comparable to those obtained in clinics and biochemical research studies. Docking studies showed that IA had estrogen receptor-positive (ER-positive) binding affinity to fulvestrant, bazedoxifene, and cyclophosphamide. This means that IA could be used to treat only ER-positive breast cancer once it has been proven to work in the clinic and received official approval.[39] Furthermore, the alkaloid and phenolic content of *Catharanthus roseus*, combined with three newly isolated dimeric indole alkaloids, including 14', 15'-didehydrocyclovinblastine, 17-deacetoxyvinamidine, and 17-deacetoxycyclovinblastine, contributes to its anticancer properties by inhibiting cell proliferation and inducing apoptosis on the MDA-MB-231 human breast cancer cell line.[38] Furthermore, *in vivo* studies reported a synergistic effect of combining *Catharanthus roseus* with *Phyllanthus urinaria*, as the chemotherapy regimen consisting of irinotecan, 5-fluorouracil, and leucovorin exhibited an immunomodulatory effect upon inhibiting the proinflammatory cytokines interleukin-17A (IL-17A) and IL-6.[40,41]

Ceratonia siliqua

Ceratonia siliqua (Carob tree) is a member of the Fabaceae family. It is a perennial evergreen tree that grows in the Mediterranean region. The highly esteemed Carob fruit, also known as a pod, is widely used as food due to its high nutritional value and as a versatile raw material in industry. This pod, which is entirely made of pulp and seeds, contains bioactive compounds beneficial for human health. In addition, although the leaves of the Carob tree are not appreciated enough for their health benefits, they contain a large number of useful compounds that have been widely used in medicinal practice.[1] *Ceratonia siliqua* is utilized by the population of Cyprus for its nutritional benefits, including the consumption of raw fruits, conversion of dried fruits into flour to alleviate gastrointestinal issues and diarrhea in infants, production of Carob molasses, and incorporation of Carob molasses into various culinary recipes.[24,42] *Ceratonia siliqua* occupies a significant place in the flora of Cyprus, as indicated by its IN status. Distributed across divisions 1, 2, 3, 4, 6, 7, and 8, as illustrated in Figure 6, this plant's presence spans various regions of the island and thrives in diverse habitats.[25] A comprehensive study exploring the medicinal potential of Carob plants native to Cyprus for the treatment of breast cancer identified high contents of myricetin, naringenin, and kaempferol, which are prominent polyphenols recognized for their anti-cancer activity, in diethyl-ether and ethyl acetate extracts obtained from ripe whole Carob fruit. These extracts exhibited specific activity against the MCF-7 breast cancer cell line. They also selectively inhibit proliferation and induce apoptosis. While exhibiting these effects, they have a minimal effect on normal cells.[43,44] Yet another study examined the ethanolic extract of *Ceratonia siliqua* extract (CSEE), which includes an array of phenolic compounds and flavonoids, in which, in addition to naringin, a significant amount was represented. CSEE treatment inhibited the proliferation of MCF-7, MDA-MB-231, and MDA-MB-436 breast cancer cells. It is clear that among these three cell lines, MCF-7 was the most responsive to CSEE treatment, whereas MDA-MB-231 and MDA-MB-436 cells exhibited fewer sensitive reactions.[1] Other than these components, the Carob leaves, pulp, and seeds contain gallic acid, chlorogenic acid, syringic acid, p-coumaric acid, m-coumaric acid, quercetin 3-O-rutinoside, and quercetin, which contribute to the nutrition of Carob pods. Upon the observation of a methanolic leaf extract of Carob, rich in significantly high amounts of these phenolic compounds, total flavonoids, and condensed tannins, it was observed that Carob extract showed a dose-dependent cytotoxic effect on MDA-MB-231 human breast cancer cells. Moreover, the leaf extracts exhibited a notable capacity to inhibit cell proliferation, resulting in an increase in the proportion of cells at the sub-G1 stage compared with the pulp extracts.[43,45]

Figure 6. *Ceratonia siliqua* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Ceratonia siliqua* in Cyprus. Areas marked in green indicate divisions where *Ceratonia siliqua* grows indigenously.[25] Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

Cicer arietinum

Cicer arietinum, a member of the Fabaceae family, is commonly referred to as desi Chickpea. In nature, the flower is noticeable by its small size and colorful seed coats of red, green, brown, and black. Global diets incorporate Chickpeas, primarily from Asia, in various forms such as cooked grains or flour.[46,47] Many bioactive compounds, especially isoflavone, are known for their strong anticancer effects by binding to ERs and working with estrogenic polyphenols.[46] Chickpeas have traditional medicinal value and have been used historically to treat health concerns ranging from hypertension to osteoporosis.[47] In Cyprus, Cicer arietinum is incorporated into the daily diet. Before serving as appetizers, these Chickpeas undergo various culinary processes such as boiling. Moreover, people consume the raw seeds of this plant for their believed aphrodisiac properties and to alleviate hoarseness.[24,42] Figure 7 shows that *Cicer arietinum* classified under the CA status is significant in the flora of Cyprus, spanning divisions 1, 2, and 3. The relevance of this approach to breast cancer research in Cyprus is compelling. This introduction outlines the significance of *Cicer arietinum* in breast cancer research within Cyprus, focusing on its botanical traits and island-wide distribution.[25] For example, research using *Cicer arietinum* on breast cancer has shown that sprouted Chickpeas increase the levels of isoflavone in black Chickpeas, which lowers the growth of MDA-MB-231 cancer cells. The isoflavone mentioned include biochanin A, genistein, formononetin, calycosa, trifolyrhizin, biochanin A-7-Ob-D-glucoside, ononis, and missouri. These isoflavone might stop the SKBr3 and MCF-7 cell lines from moving through the cell cycle or multiplying in a way that depends on time and dose by changing signaling pathways.[47,48] They also have strong antitumor effects on MDA-MB-231 cancer cells, causing mitochondrial-dependent apoptosis, stopping cell growth, stopping cell adhesion, and changing the shape of the cells.[49] Here, the study identified that the NF-kB signaling pathway, which regulates critical

Figure 7. *Cicer arietinum* photograph in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Cicer arietinum* in Cyprus. Areas marked in yellow indicate divisions where *Cicer arietinum* grows casually (CA).[25] Photographer: G. N. Hadjikyriakou.

biological processes like proliferation and apoptosis, as a common active pathway in MDA-MB-231 cancer cells.[46,49] Lectin from Chickpeas prevents MCF-7 cells from dividing and apoptosis in the S and G2 phases of the cell cycle. On the other hand, protease inhibitors effectively kill MDA-MB-231 breast cancer cells, possibly by interfering with certain cellular processes or pathways.[48]

Citrullus colocynthis

Citrullus colocynthis, classified as Bitter apple or colocynth, is a subtropical desert viny plant that grows in arid and sandy soil across the Mediterranean and Asian Basins as part of its global distribution.[50] Bitter apple is a typical wild species of the family Cucurbitaceae, and it is well-known for its variety of genetic strains.[51] *Citrullus colocynthis* fruit, which has a naturally spherical yellowish-brown appearance, contains various bioactive elements that have beneficial effects on human health.[52] Traditional medicine uses the roots, stems, fruits, and leaves of this medicinal plant to alleviate a variety of health problems, including bacterial infections and cancer.[15,53,54] The local people of Cyprus primarily use this medicinal plant by boiling its roots and then drinking it after cooling down for its purgative effect.[24,42] *Citrullus colocynthis* occupies a leading place among Cyprus's flora species under the status of IN. As shown in Figure 8, this medicinal plant is distributed across divisions 1, 5, and 7 of the island.[25] In studies, both ethanolic and aqueous extracts from fruit flesh showed great potential, with over 50% reduction in cell survival rates observed in MCF-7 breast cancer cell lines.[52,53,55] Moreover, cucurbitacin glycoside, derived from the leaves of *Citrullus colocynthis,* has been identified as an effective agent for treating human breast cancer cells because it causes apoptosis and cell cycle arrest.[15,50,53,56] The cells, which contained cucurbitacin glucosides, showed these effects as they quickly reduced the levels of these proteolytic complexes that are essential for the regulation of G2 progression and subsequent M-stage beginning.[50] Additionally, the ethanol extract of seeds was found to be toxic to MDA-MB-231 cells via the presence of components such as ethylbenzene and tetrachloroethylene[15], while the ethanol extract of leaves induced cell death in the MCF-7 cells via the regulation of the expression of pro-apoptotic (*Bax*) and *caspase-3* genes.[57,58] Methanolic extracts of *Citrullus colocynthis* leaves appeared to be very promising as breast cancer therapy agents, as they demonstrated dose- and time-dependent cytotoxic effects by increasing caspcaspase-3e expression

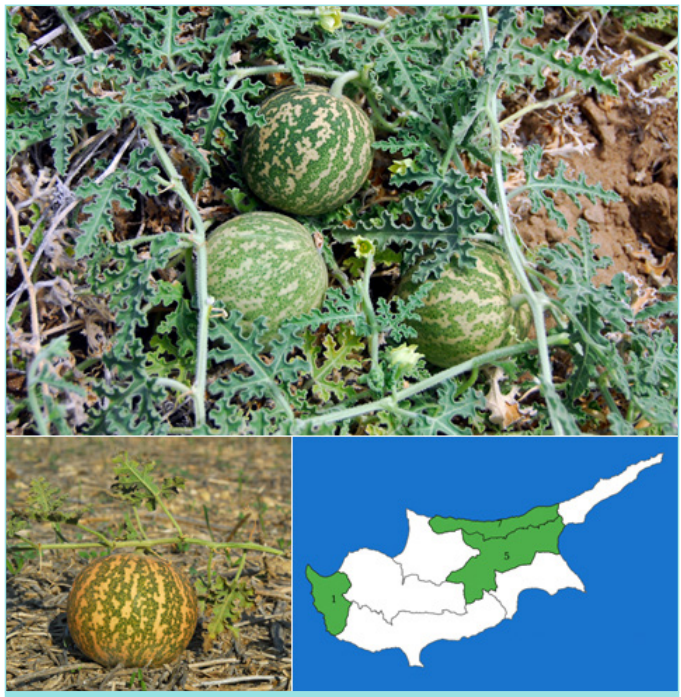

Figure 8. *Citrullus colocynthis* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Citrullus colocynthis* in Cyprus. Areas marked in green indicate divisions where *Citrullus colocynthis* grows indigenously.[25] Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

level MCF-7 cells and slowing down cell proliferation markers like Ki67 in a dose-dependent manner.[54,59] In addition, higher cholesterol levels stimulated the development of breast cancer. Breast cancer cells can be altered to downregulate de novo the petty acid synthesis pathway, which is thus interfered with via the use of *Citrullus colocynthis* leaf extract to regulate cholesterol and triglyceride levels, which were the primary objective.[59] In addition, experiments demonstrating the effectiveness of evodiamine in combination with berberine demonstrated that MCF-7 breast cancer cells were arrested in the cell cycle while reducing the expression of proteins responsible for cell cycle progression.[54] Moreover, as exhibited by the *Citrullus colocynthis*-linked silver nanoparticles, the antiproliferative effect in MCF-7 cells was through the interference of both cholesterol and triglyceride levels, thus showing potential in the management of breast cancer advancement.[51]

Ficus carica

Ficus carica, commonly known as the Fig, belongs to the Moraceae family.[60] The figure, as a seasonal fruit, is one of the earliest cultivated species and is an important crop globally, flourishing within the natural ecosystems of the Mediterranean basin.[61,62] *Ficus carica* has a variety of applications in Cypriot traditional medicine, including its use as a remedy for insect bites by preparing leaf decoctions and applying them externally to affected areas. Additionally, the latex derived from cutting branches is used topically to alleviate skin infections, demonstrating the plant's therapeutic efficacy within local healing practices.[24,42] The classification of *Ficus carica* is shown in Figure 9, where IN indicates its widespread distribution across divisions 1, 2, 3, and 5. Exploring the therapeutic potential of *Ficus carica* in breast cancer research holds promise for uncovering novel treatments deeply rooted in Cyprus's

botanical heritage.[25] The ethanol extract of *Ficus carica* leaves exhibited notable anticancer activity against MCF-7 cells. The presence of secondary metabolites, specifically flavonoids and tannins, in Fig leaf and fruit extracts is responsible for this effect.[61,63] Using *Ficus carica* leaf latex, which is full of alkaloids, polyphenols, and hydrolytic enzymes, to treat MDA-Mb-231 cells decreased the levels of ERK2, CREB, and AKT2. This suggests that the latex can be used to treat breast cancer. The Figure latex also prevented the growth of large tumors without affecting hematologic parameters or inflammation. This is because it has antioxidant, anti-inflammatory, and pro-apoptotic properties. In experiments with rats, *Ficus carica* latex extract reduced breast tumor volume and size. It suggests that reduced angiogenesis, mitotic activity, and necrosis are potentially mediated by its active ingredients.[60,64,65] A different study found that treating MDA-MB-231 cells with *Ficus carica* extract prevented them from multiplying while leaving MCF10A normal breast epithelial cells alone. Bergapten and psoralen, two active ingredients in *Ficus carica* leaves, were found to have similar anticancer effects, especially in MDA-MB-231 cells. In treated cells, these effects included increased expression of apoptosis-promoting genes, cell-cycle arrest at the S phase, and reduced cell mobility.[62,63]

Glycyrrhiza glabra

The pharmaceutical, nutritional, and occasionally even tobacco industries highly value the perennial herb known scientifically as *Glycyrrhiza glabra*, a member of the Fabaceae family. The Greek meaning of its name, glycosmis (sweet) and riza (root), add to its significance. The first thing to think about is *Glycyrrhiza glabra*, which is usually recognized by its smooth, crack-free fruit and glycyrrhizin, which is its main chemical and is over 50 times sweeter than sugar.[66] Interestingly, glycyrrhizin production rises as the plant's age increases in years.[67] Herbal remedies have been studied for the treatment of various diseases based on the healing properties of their roots and stems.[66,67] Studies have demonstrated its traditional value, revealing anti-fungal, antihepatotoxic, and anti-cancer effects due to its bioactive compounds.[68] The local people of Cyprus generally use *Glycyrrhiza glabra* daily due to its sweetening and flavoring properties. In addition, the preparation of syrup from the roots serves as a cough suppressant.[42] The flowers of Cyprus hold a significant role in the medicinal production of the *Glycyrrhiza glabra* plant, known as IN. Its presence spans divisions 3, 4, 5, and 7, as shown in Figure 10, indicating its distribution across specific regions of the island.[25] Research has demonstrated that *Glycyrrhiza glabra* extract regulates the metabolism of genotoxic estrogen, enhance the metabolism of harmless estrogen, enhance detoxification enzymes, prevents DNA damage, and ultimately suppresses inflammation.[69] As the same cancer cell line was commented the glycyrrhizin derivative, 3-acetyl-18-glycyrrhetinic-30-methyl ester, triggered apoptosis in the same cancer cell line by activating caspases and altering the conformation.[70] Furthermore, reports have suggested that glycyrrhizin inhibits metastasis, invasion, and new blood cell formation in human MDA-MB-231 cancer cells. Reports have indicated that inhibition of the FAK/Rho signaling pathway achieves this effect.[71] On the other hand, mean glycyrrhizin is effective at stopping the growth of MDA-MB-231. It even increases the levels of miR-200c and e-cadherin, which are known to prevent cancer cells from spreading and invasiveness.[71,72] The root extract of *Glycyrrhiza glabra* influences the model by reversing the viability and inducing morphological changes in the mammary cell lines 4T1, MCF-7, and HER-2. Additionally, it enhances the phosphorylation level of Bcl. Furthermore, glycyrrhizin targets growth inhibition, followed by breast tumor outgrowth and pulmonary metastasis via *p38 MAPK-AP1* gene pathway modification.[72] Findings indicate two things: Firstly, the watery extract of Licorice contains phytoestrogen compounds that can help prevent cancer. Secondly, the use of Licorice compounds along with chemotherapeutic agents is better for the treatment.[68] Patients with breast cancer can also use glycyrrhetinic acid from *Glycyrrhiza glabra* root as an alternative to doxorubicin, which affects the mitochondrial-dependent apoptotic pathway and downregulates the VEGFR2 pathway.[73]

Hordeum vulgare

Barley is a cereal plant type with the scientific name *Hordeum vulgare* and belongs to the family Poaceae. It has inherited the ancient belief of traditional medicine that its properties are cold and dry, due to which it has a purifying power.[11,48,74] As the fourth largest cereal crop worldwide, Barley has been used for years not only as animal feed and in alcoholic brewing but also as a diet health supplement because it contains many natural nutrients like Barley juice and young leaves, which are used as its plant metabolite products.[74] Traditionally, it has been used to treat a wide range of diseases, such as diabetes, respiratory illnesses, arthritis, and obesity.[11,48,74] Other uses of Barley

Figure 9. *Ficus carica* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Ficus carica* in Cyprus. Areas marked in green indicate divisions where *Ficus carica* grows indigenously.[25] Photographer: G. N. Hadjikyriakou and C. S. Christodoulou.

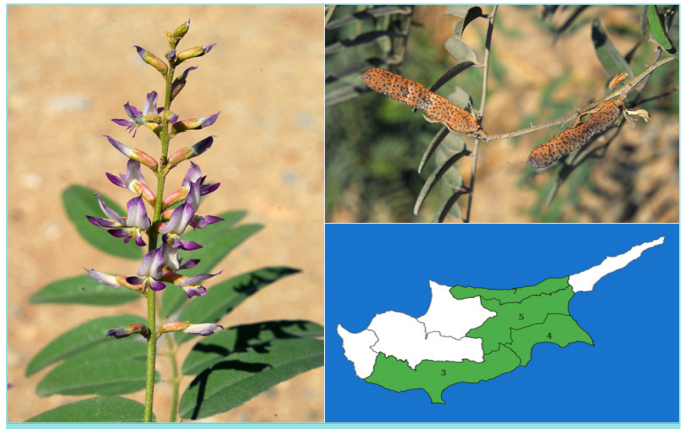

Figure 10. *Glycyrrhiza glabra* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Glycyrrhiza glabra*. Areas marked in green indicate divisions where *Glycyrrhiza glabra* grows indigenously.[25] Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

include its flowers as a contraceptive and dried seeds as an infusion to exhibit galactagogue properties.[11] The local people of Cyprus used *Hordeum vulgare* for various purposes. Its most common use is to grind Barley and mix it with olive oil, milk, mallow, and nettle to make a paste. People apply this poultice to aching joints, anticipating its pain-reducing and antirheumatic effects.[24,42] The dynamic checklist "Flora of Cyprus" categorizes *Hordeum vulgare* as CA and reports its presence in division 2 (Figure 11).[25] A study on Barley grass extract showed that it can help fight breast cancer. This effect occurred by raising the levels of ROS in MDA-MB-231 breast cancer cells, which led to cell death. In addition, gramine, an indole alkaloid that is normally found in *Hordeum vulgare*, can stop MDA-MB-231 and MCF-7 cell growth by activating adiponectin receptor 2.[48] This is what this receptor does to the body. Further investigation using a methanol extract from germinated seeds of *Hordeum vulgare* (MGHV) will shed more light on its potential to combat breast cancer in TNBC cells. The high content of hordenine, a chemical with anticancer mechanisms that binds specifically to caspase-8 in MDA-MB-231 cells, is primarily responsible for MGHV's ability to trigger the extrinsic pathway of apoptosis without causing DNA damage.[74] Barley bran stands out among other cereal grains because it is rich in polyphenols (which include saponins, tannins, flavonoids, phenols, alkaloids, terpenoids, steroids, and carbohydrates). In addition to breast cancer treatment, it plays an important role in preventing breast cancer initiation and progression. Various Barley bran extracts cause a dose-dependent reduction in the viability of breast cancer cells. For instance, n-hexane and methanol extracts can disrupt the proliferation of both MCF-7 and EMT6/p breast cancer cells. The aqueous extract inhibited only EMT6/p breast cancer cells. Apoptosis-related proteins like caspase-3, 9, Bax, and p53 were activated by palmitic acid in another experiment. This stopped the growth of MCF-7 breast cancer cells. Studies conducted using fermented Barley extract concluded that it is not toxic to healthy cells and has the potential to prevent the progression of non-invasive breast cancer into invasive breast cancer.[75] Furthermore, scientists have noticed that the bioactive components of Barley have anti-breast cancer activity, induction of cell cycle arrest, apoptosis progression, and blockage of proliferation. The anti-breast tumor potential of young Barley and its methanolic extract is multifaceted, including mechanisms of cell apoptosis and cell growth regulation. The downregulation of tumorigenesis and upregulation of apoptosis, demonstrated by an increase in caspase-3/caspase-7 activity and a decrease in Ki67 levels in animal models, are evident.[76]

Figure 11. *Hordeum vulgare* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Hordeum vulgare* in Cyprus. The yellow area indicates the division where *Hordeum vulgare* grows casually (CA).[25] Photographer: G. N. Hadjikyriakou.

Myrtus communis

Myrtus communis, commonly known as Myrtle, a prominent member of the Myrtaceae family, is a significant aromatic and medicinal species found abundantly across Mediterranean regions.[77-79] It has a perennial bush-like form, typically with characteristic white flowers and blue ball-shaped fruits.[67,79] Because of its diverse bioactive constituents, this herbaceous plant has been integral to ancient healing practices, particularly in Greek and Unani medicine. Studies have underscored its multifaceted pharmacological effects, ranging from antimicrobial and antifungal to hepatoprotective and anticancer activities.[77,78] Additionally, daily culinary applications of *Myrtus communis* include flavoring foods and wines.[77] *Myrtus communis* is a plant that the local people in Cyprus respect for its versatile therapeutic properties, as well as its daily consumption throughout the season. People often prepare its leaves as infusions or decoctions, make them into tea, and consume them for their antihypertensive, antihyperglycemic, and cholesterol-lowering properties. Additionally, when dried in the shade and ground into a fine powder, the leaves work topically to relieve diaper rash. Additionally, consumption of its fruits has been shown to have an anti-diarrheal effect.[24,42] Figure 12 shows the distribution of *Myrtus communis* throughout the island (divisions 1, 2, 3, 4, 5, 6, 7, and 8), which earned the status of IN.[25] Due to its simple accessibility within the island and its high therapeutic effect, studies and medical advances are important. Studies have shown that *Myrtus communis* essential oil has strong cytotoxic effects against breast cancer cell lines, stopping tumor cells in a way that depends on the dose.[78-80] Furthermore, researchers concluded that this cytotoxic effect specifically targeted cancer cells, inducing apoptotic cell death through DNA fragmentation characteristics.[78] Another study showed that *Myrtus communis* essential oil is rich in alpha-pinene, 1,8-cineole, and linalool substances. The results also show that these ingredients affect MCF-7 and healthy cells

(MCF10A) in a different manner. The researchers found that α-pinene and linalool were both harmful to both types of cells. On the other hand, 1,8-cineole was only harmful to tumor cells, killing them through apoptosis, without damaging normal cells.[67,79] Another study also mentioned the importance of the essential oil had β-ionone because it had anti-cancer properties and inhibits the growth of breast cancer cells both *in vivo* and *in vitro*.[80,81] Another study showed that myrtucommulone from *Myrtus communis* leaves enhanced the activity of caspases 3 and 9, leading to poly (ADP-ribose) polymerase cleavage and apoptotic DNA fragmentation. Moreover, the methanolic extracts of *Myrtus communis* exhibited strong anticancer activity against MCF-7 cell lines.[67,78]

Nigella sativa

Nigella sativa, also known as Black cumin, is a plant that belongs to the Ranunculaceae family.[82,83] As an integral part of the healing process, *Nigella sativa* has been used in the medical systems of many cultures and cuisines.[82,84] Many active compounds, including thymol, dithymoquinone, thymoquinone, and thymohydroquinone, contribute to its broad spectrum of pharmacological functions, including anti-inflammatory, antihypertensive, antioxidant, antidiabetic, antimicrobial, and anticancer properties.[63,83,85,86] *Nigella sativa* use among Cyprus's population encompasses diverse medicinal applications. Local people incorporated decoction tea derived from the seeds internally because of its purported antihyperglycemic, cholesterol-lowering, and carminative properties.[42] *Nigella sativa* is a noteworthy subject in the context of medicinal plants found in Cyprus. This plant, classified as CA in divisions 2, 3, and 7 (Figure 13), is consistent with the vibrant colors of Cyprus's natural landscape during the warmer months. *Nigella sativa* has a rich historical and cultural significance and is revered for its numerous health benefits and therapeutic properties.[25] Numerous studies have investigated the potential of *Nigella sativa* in the treatment of breast cancer. The watery and rough extracts of *Nigella sativa* are effective at stopping the growth of MCF cell lines. Histological studies on DMBA-treated rats have shown that *Nigella sativa* can activate breast cells and stop cancer cell growth.[63,86] Thymoquinone is a key compound in *Nigella sativa* seed oil that has been shown to reduce the size of tumors and change gene expression, including increasing *p53* expression and decreasing *BRCA1* and *BRCA2*.[63,85,86] Furthermore, the application of nanosized emulsions and aqueous extracts from *Nigella sativa* can induce apoptosis in MCF-7 cells. Consequently, the application of nanosized emulsions and aqueous extract of *Nigella sativa* prevents MCF-7 cell viability.[63,83,85] Additionally, studies have demonstrated that *Nigella sativa* silver nanoparticles trigger programmed cell death through the up- or downregulation of Bax, Bcl-2, and cyclooxygenase-2 (Cox-2).[63,83] In addition, thymoquinone can inhibit metastasis by suppressing CXCR4 expression and decreasing movement and metastasis in breast cancer cell lines.[82,85] When thymoquinone is combined with the common drug tamoxifen, they work together to kill more cells and cause more cell death in both ER positive and ER negative cells.[85] In addition, nanostructured lipid carriers loaded with thymoquinone changed the cell genome and killed MDA-MB-231 and MCF-7 cells. In contrast, the pure extract of *Nigella sativa,* which is rich in calcium and magnesium, induces apoptosis by proliferating inside the cells.[85,86]

Olea europaea

Olea europaea, commonly known as the Olive tree, is an important staple crop in the Mediterranean Basin that has attracted great attention in daily life and medicine because of the oil obtained from its fruits and leaves, which contain various bioactive compounds.[2,87] Studies dating back to the present day have revealed the existence of antimicrobial, antioxidant, antitumor, and hypoglycemic effects of compounds obtained from this plant's parts.[2,87,88] *Olea europaea* serves various purposes for local people in Cyprus, including nutrition and medicinal applications. The daily diet incorporates fruits, such as olives, whether black or green. Additionally, its leaves are boiled and consumed for their cholesterol-lowering effects. Olive oil is applied topically to alleviate pain, particularly in cases of sprained ankles. Moreover, it is used to induce emesis by mixing it with milk and consuming it in cases

Figure 12. *Myrtus communis* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Myrtus communis* in Cyprus. Areas marked in green indicate divisions where *Myrtus communis* grows indigenously.[25] Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

Figure 13. *Nigella sativa* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Nigella sativa* in Cyprus. The yellow area indicates the division where *Nigella sativa* grows casually (CA).[25] Photographer: G. N. Hadjikyriakou.

of poisoning.[24,42] *Olea europaea* is a significant flora of Cyprus, denoted by its status as an IN species. The plant distribution, as shown in Figure 14 across divisions 1, 2, 3, 4, 7, and 8 elucidates its prevalence in various regions of the island, ranging from coastal areas to mountainous terrain.[25] Studies have investigated the potential anticancer activity of *Olea europaea*, particularly its constituent oleuropein (OLE).[87,89,90] OLE has been shown to exhibit a dose- and time-dependent decrease in the viability of MCF-7 breast cancer cells and a synergistic inhibitory effect with metformin.[2] Notably, OLE exhibited apoptotic and anti-invasive effects on MCF-7 cells, modulating histone deacetylase (HDAC) activity. The outgrowth processes, including the diminished level of invasiveness, the boost of apoptosis, and the inhibition of proliferation, are likely to take place in a setting of HDAC4 expression reduction.[87,90,91] Additionally, OLE initiates the ERK1/2 inhibition action via estradiol communication; additionally, it causes apoptosis through the NF-κB activation and inactivation pathways in MDA-MB-231 and MCF-7 cell cultures. The combined therapeutic system of doxorubicin and OLE will increase the effectiveness of both drugs and eventually produce downregulation of NF-κB, Bcl-2, and survivin, which causes the cell to enter the apoptosis process and, hence, a decrease in tumor size in MDA-MB-231 breast cancer. In addition, oleocanthal can block the proliferation of breast cancer cell lines such as MCF-7, BT474, and MDA-MB-231, whereas normal cell growth was not affected.[88,89,91] Another example of chemo-preventive phytochemicals is apigenin in *Olea europaea* leaves, and hydroxytyrosol in both leaves and oils from this plant, which can exert an antitumor effect by targeting growth factor receptors and interleukin pathways that result in cell cycle arrest at the G2/M and G1/S phases of the MCF-7 cell line.[88,91]

Rosmarinus officinalis

Rosmarinus officinalis is a member of the Lamiaceae family and is one of the most helpful evergreen medicinal plants known as Rosemary.[92,93] It is a common herb that originated in the Mediterranean.[93,94] This plant has distinctive needle-like dark green leaves. Due to its valuable medicinal qualities, people not only use its small, needle-shaped dark green leaves for flavoring dishes and seasonings but also for therapeutic purposes. People continue to use it to target various diseases, such as tumor proliferation, and because of its anticancer, antithrombotic, anti-inflammatory, hepatoprotective, antidiabetic, antibacterial, and antihypertensive properties.[92,93] The local people in Cyprus use *Rosmarinus officinalis* primarily for its multifaceted healing properties. The diuretic action and cholesterol-lowering activity of Rosemary tea regulate digestive system functioning and improve circulatory organ health. Additionally, it serves as an expectorant for patients with bronchitis and is preferred due to its ability to act as an analgesic for those suffering from migraines and/or stomach pain. Additionally, previous studies have shown that inhaling steam from a Rosemary infusion alleviates cold symptoms.[24,42] In divisions 1 and 8, of Cyprus categorize *Rosmarinus officinalis* as IN (Figure 15). With its aromatic foliage and diverse array of bioactive compounds, Rosemary is a botanical treasure trove, offering potential avenues for exploring its efficacy in combating breast cancer.[25] *Rosmarinus officinalis* attracts uric acid, rosmarinic acid, carnosic acid, oleanolic acid, and betulinic acid, all of which have specific effects on cancer cells.[93-95] A dose-response protocol revealed that Rosemary essential oil induces apoptosis in MCF-7 cells. In addition, Rosemary oil has different cytotoxic effects on different types of cancer cells. For example, flavonoids can stop the expression of Cox-2, which is an important enzyme involved in the progression of breast cancer. Moreover, carnosol and uric acid suppress the DNA-binding activity of cancer cells and block tumorigenesis pathways, including those that NF-B modulates.[63,95] Researchers highlighted the cancer-inhibitory functions of carnosic acid, particularly its ability to destroy tumor-resistant cells. This suggests that it is suitable as a complementary treatment.[94,95] Furthermore, green synthesized silver nanoparticles derived from Rosemary exert cytotoxic effects on breast cancer, potentially inhibiting the progression of the disease.[92] Most importantly, studies have shown that rosmarinic acid, a natural polyphenol compound, exerts powerful anticancer activity against TNBC cells such as MDA-MB-231 and MDA-MB-468.[96] The diverse regulation of numerous apoptosis-related gene sequences, particularly in MDA-MB-468 cells, demonstrates the activity of rosmarinic acid.

Figure 14. *Olea europaea* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Olea europaea* in Cyprus. Areas marked in green indicate divisions where *Olea europaea* grows indigenously.[25] Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

Figure 15. *Rosmarinus officinalis* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Rosmarinus officinalis* in Cyprus. The area marked in green indicates the division where *Rosmarinus officinalis* grows indigenously, and the area marked in orange indicates the division where it is naturalized.[25] Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

These findings underscore the therapeutic potential of Rosemary and its constituents in breast cancer management, particularly in TNBC therapy.[10]

Silybum marianum

Silybum marianum, commonly referred to as Milk thistle, is well-known in traditional medicine because of its over 2000 years of use by many people.[97,98] The Milk thistle, a relative of the Asteraceae family, originated in the mountainous regions of the Mediterranean.[98,99] People have revered Milk thistle for its efficacy in treating liver and gallbladder-related ailments.[12,98,100] As a traditional edible phytomedicine, Milk thistle has maintained its significance as a natural remedy for conditions such as hepatitis and cirrhosis.[12,100,101] Local people in Cyprus use the Milk thistle plant in their daily medicinal practices to treat skin wounds and foot fungal ailments. The plant demonstrates its healing effect by extracting the bulbous part with a hoe and then applying its peels to the affected area while still moistened.[24] In Figure 16, the status of *Silybum marianum* is shown as IN and its presence in divisions 2, 3, 4, 5, 6, and 8 of Cyprus. In a previous study, it was observed that silymarin, a powerful polyphenol from the medicinal plant *Silybum marianum*, exhibited significant activity against MDA-MB-468 and MCF-7 breast. These cells respond to silymarin by arresting the cell cycle and inducing apoptotic cell death. Mechanisms involving increased p53 expression and downregulation of vascular endothelial growth factor and matrix metalloproteinase/gelatinase A mediate the effects of this compound.[12,100] Another study found that silymarin stops the growth of MDA-MB-468 breast cancer cells by stopping them in the G1 cell cycle.[99] Furthermore, *Silybum marianum* seed aqueous extract is cytotoxic in human breast cancer cell lines, altering cell viability in a manner reliant on time and concentration.[12] Additionally, studies have shown that silibinin, a component of silymarin, exhibits dose- and time-dependent reduction in MCF-7 cells and exhibits synergistic effects when used with ultraviolet B and other chemotherapeutic agents.[100] Moreover, spherical liposome-encapsulated silibinin nanoparticles have been observed to stimulate MCF-7 cell growth and induce apoptosis more efficiently than drug monotherapy, indicating the potential of nanoparticles in breast cancer treatment.[102] Interestingly, silibinin exhibits a synergistic effect with several chemotherapeutic agents, such as carboplatin, doxorubicin, or cisplatin-all of which significantly depend on estrogens-in breast cancer cells. This further demonstrates the potential of silibinin as an adjunct in breast cancer therapy.[101]

Figure 16. *Silybum marianum* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Silybum marianum* in Cyprus. Areas marked in green indicate divisions where *Silybum marianum* grows indigenously.[25] Photographer: G. N. Hadjikyriakou.

CONCLUSION

Breast cancer remains one of the leading health threats globally, with its trends in incidence and mortality rates continuing to persist and requiring further improvements in treatment approaches. Treatments such as chemotherapy, radioactive cancer therapy, and surgery are effective; however, they often have severe adverse effects that significantly impact patients' quality of life. As a result, there has been an increasing emphasis on investigating other forms of treatment, particularly those that consider natural sources such as medicinal plants. This review highlights medicinal plants found in Cyprus that have shown some effectiveness as anti-breast cancer agents. Reports indicate that the bioactive compounds in these plants suppress the growth of cancerous cells, induce programmed cell death, and prevent cancer cell spread. These bioactive compounds are potential novel anti-breast cancer agents. Therefore, isolating and standardizing these compounds could lead to new treatment approaches that can be used as effective adjuvant therapy to traditional cancer treatment methods. As a result of further research, integrating such medicinal plants into breast cancer treatment may increase treatment effectiveness, which may improve the well-being of breast cancer patients; this highlights the importance of further studies on the medicinal flora of Cyprus and its potential benefits in oncology.

MAIN POINTS

- Breast cancer remains a major global health issue, with current treatments like chemotherapy, radiation, and surgery, are effective, but they often cause severe side effects that reduce patients' quality of life.
- Due to the side effects of traditional treatments, there is growing interest in exploring natural alternatives, particularly medicinal plants, as cancer treatments.
- This study highlights several plants found in Cyprus that have shown promise as anti-breast cancer agents. Secondary metabolites were explored from medicinal plants as safer alternatives to conventional treatments. These plant compounds have shown promise in preventing cancer cell growth and promoting cell death, offering a potential way to treat breast cancer with fewer side effects.
- If these plant compounds are further researched and standardized, they could become new treatments or be used alongside traditional therapies to improve patient outcomes and well-being, making it important to continue studying Cyprus' medicinal plants for their potential in cancer care.

Footnotes

Authorship Contributions

Concept: G.O., Design: G.Ç., G.O., Data Collection or Processing: G.Ç., Analysis and/or Interpretation: G.O., M.Ç., S.R., Literature Search: G.Ç., Writing: G.Ç., G.O., M.Ç., S.R.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

REFERENCES

1. Anago AD, Gaetan Segbo JA, Gnangnon F, Akpovi CD, Agbangla C. Some medicinal plants with anti-breast cancer activity and the input of phytotherapy in the treatment of breast cancer. ESJ. 2023; 19(18): 66.
2. Quattrocchi A, Demetriou CA, Cory OA, Saad B, Constantinou C, Marcou Y, et al. Breast cancer trends in women in Cyprus: a population-based study between 2004-2017. Eur J Public Health. 2022; 32(Suppl 3): ckac131.141.
3. Elbouzidi A, Taibi M, Ouassou H, Ouahhoud S, Ou-Yahia D, Loukili EH, et al. Exploring the multi-faceted potential of carob (ceratonia siliqua var. rahma) leaves from morocco: a comprehensive analysis of polyphenols profile, antimicrobial activity, cytotoxicity against breast cancer cell lines, and genotoxicity. Pharmaceuticals (Basel). 2023; 16(6): 840.
4. Isleem RM, Alzaharna MM, Sharif FA. Synergistic anticancer effect of combining metformin with olive (Olea europaea L.) leaf crude extract on the human breast cancer cell line MCF-7. Journal of Medicinal Plants Studies. 2020; 8(2): 30-7.
5. Zanti M, Loizidou MA, Michailidou K, Pirpa P, Machattou C, Marcou Y, et al. NGS panel testing of triple-negative breast cancer patients in cyprus: a study of BRCA-negative cases. Cancers (Basel). 2020; 12(11): 3140.
6. Iqbal J, Abbasi BA, Mahmood T, Kanwal S, Ali B, Shah SA, et al. Plant-derived anticancer agents: a green anticancer approach. Asian Pacific Journal of Tropical Biomedicine. 2017; 7(12): 1129-50.
7. Li X, Zhou J, Wang X, Li C, Ma Z, Wan Q, et al. New advances in the research of clinical treatment and novel anticancer agents in tumor angiogenesis. Biomed Pharmacother. 2023; 163: 114806.
8. Buyel JF. Plants as sources of natural and recombinant anti-cancer agents. Biotechnol Adv. 2018; 36(2): 506-20.
9. Greenshields AL, Fernando W, Hoskin DW. The anti-malarial drug artesunate causes cell cycle arrest and apoptosis of triple-negative MDA-MB-468 and HER2-enriched SK-BR-3 breast cancer cells. Exp Mol Pathol. 2019; 107: 10-22.
10. Messeha SS, Zarmouh NO, Asiri A, Soliman KFA. Rosmarinic acid-induced apoptosis and cell cycle arrest in triple-negative breast cancer cells. Eur J Pharmacol. 2020; 885: 173419.
11. Abuarab SF, Talib WH. Immunomodulatory and anticancer activities of barley bran grown in Jordan: an in vitro and in vivo study. Front Nutr. 2022; 9: 838373.
12. Jao HY, Chang FR, Cheng CW, Liang HW, Wang CJ, Lee HJ. Silybum marianum seed disrupts mitosis by reducing polo-like kinase 1 in breast cancer cells. Phytomedicine Plus. 2022; 2(1): 100164.
13. Cruceriu D, Balacescu O, Rakosy E. Calendula officinalis: potential roles in cancer treatment and palliative care. Integr Cancer Ther. 2018; 17(4): 1068-78.
14. Munir A, Fatima I, Humma Z. Evaluation of therapeutic potential of natural resources against breast cancer. Pakistan Journal of Biochemistry and Biotechnology. 2022; 3(2): 89-101.
15. Bourhia M, Messaoudi M, Bakrim H, Mothana RA, Sddiqui NA, Almarfadi OM, et al. Citrullus colocynthis (L.) Schrad: Chemical characterization, scavenging and cytotoxic activities. Open Chemistry. 2020; 18(1): 986-94.
16. Wu TN, Chen HM, Shyur LF. Current advancements of plant-derived agents for triple-negative breast cancer therapy through deregulating cancer cell functions and reprogramming tumor microenvironment. Int J Mol Sci. 2021; 22(24): 13571.
17. Khan T, Ali M, Khan A, Nisar P, Jan SA, Afridi S, et al. Anticancer plants: a review of the active phytochemicals, applications in animal models, and regulatory aspects. Biomolecules. 2020; 10(1): 47.
18. Chrysargyris A, Petrovic JD, Tomou EM, Kyriakou K, Xylia P, Kotsoni A, et al. Phytochemical profiles and biological activities of plant extracts from aromatic plants cultivated in Cyprus. Biology. 2024; 13(1): 45.
19. Achilonu MC, Ngubane XV, Nkosi SM, Jiyane PC. Phytochemicals, bioactivity, and ethnopharmacological potential of selected indigenous plants. S Afr J Sci. 2023; 119(1/2).
20. Hadjichambis AC, Dimopoulos P, Georghiou K. Utilization of the flora in ecological evaluation of the dune ecosystems using ecological indices. 2006. Available from: http://rgdoi.net/10.13140/2.1.4335.6808
21. Sánchez M, González-Burgos E, Iglesias I, Gómez-Serranillos MP. Pharmacological update properties of aloe vera and its major active constituents. Molecules. 2020; 25(6): 1324.
22. Tong X, Li M, Li D, Lao C, Chen J, Xu W, et al. Aloe vera gel extract: safety evaluation for acute and chronic oral administration in Sprague-Dawley rats and anticancer activity in breast and lung cancer cells. J Ethnopharmacol. 2021; 280: 114434.
23. Ur Rehman N, Halim SA, Khan M, Hussain H, Yar Khan H, Khan A, et al. Antiproliferative and carbonic anhydrase II inhibitory potential of chemical constituents from lycium shawii and aloe vera: evidence from in silico target fishing and in vitro testing. Pharmaceuticals (Basel). 2020; 13(5): 94.
24. Kaya Yıldırım F. Kuzey Kıbrıs'ın faydalı bitkilerinin ve kullanım alanlarınınaraştırılması [Yüksek Lisans Tezi]. Yakın Doğu Üniversitesi; 2010.
25. Hand R, Hadjikyriakou GN, Christodoulou CS. Flora of Cyprus-a dynamic checklist. Flora of Cyprus. 2011. Available from: https://www.flora-of-cyprus.eu/
26. Ali K, Saquib Q, Siddiqui MA, Ahmad J, Al-Khedhairy AA, Musarrat J. Anti-cancer efficacy of Aloe vera capped hematite nanoparticles in human breast cancer (MCF-7) cells. Journal of Drug Delivery Science and Technology. 2020; 60: 102052.
27. Majumder R, Parida P, Paul S, Basak P. In vitro and in silico study of Aloe vera leaf extract against human breast cancer. Natural Product Research. 2020; 34(16): 2363-6.
28. Mandrich L, Piccolella S, Esposito AV, Costa S, Mercadante V, Pacifico S, et al. Different extraction procedures revealed the anti-proliferation activity from vegetable semi-purified sources on breast cancer cell lines. Antioxidants. 2023; 12(6): 1242.
29. Ekiert H, Świątkowska J, Klin P, Rzepiela A, Szopa A. Artemisia annua-importance in traditional medicine and current state of knowledge on the chemistry, biological activity and possible applications. Planta Med. 2021; 87(08): 584-99.
30. Ko YS, Jung EJ, Go S il, Jeong BK, Kim GS, Jung JM, et al. Polyphenols extracted from artemisia annua l. exhibit anti-cancer effects on radio-resistant MDA-MB-231 human breast cancer cells by suppressing stem cell phenotype, β-catenin, and MMP-9. Molecules. 2020; 25(8): 1916.

31. Lang SJ, Schmiech M, Hafner S, Paetz C, Steinborn C, Huber R, et al. Antitumor activity of an Artemisia annua herbal preparation and identification of active ingredients. Phytomedicine. 2019; 62: 152962.

32. Lang SJ, Schmiech M, Hafner S, Paetz C, Werner K, El Gaafary M, et al. Chrysosplenol d, a flavonol from artemisia annua, induces ERK1/2-mediated apoptosis in triple negative human breast cancer cells. Int J Mol Sci. 2020; 21(11): 4090.

33. Alsaraf KM, Mohamed MH, Al-Shammari AM, Abbas IS. Broad-spectrum cytotoxic effect of calendula officinalis L against breast cancer cells. Indian Journal of Forensic Medicine and Toxicology. 2020; 14(1): 803-809. 10.37506/v14/i1/2020/ijfmt/193002.

34. Cruceriu D, Diaconeasa Z, Socaci S, Socaciu C, Rakosy-Tican E, Balacescu O. Biochemical profile, selective cytotoxicity and molecular effects of Calendula officinalis extracts on breast cancer cell lines. Notulae Botanicae Horti Agrobotanici Cluj-Napoca. 2020; 48(1): 24-39.

35. Zhai C, Shi C, Hu Y, Xu Z, Wang R. Anti-breast carcinoma effects of green synthesized tin nanoparticles from Calendula officinalis leaf aqueous extract inhibits MCF7, Hs 319.T, and MCF10 cells proliferation. Journal of Experimental Nanoscience. 2022; 17(1): 351-61.

36. Jodh R, Tawar M, Behere S, Randhave N, Jirapure P, Ingle S. A review on calendula officinalis. Research Journal of Pharmacognosy and Phytochemistry. 2023; 15(1): 5-10.

37. Siti Z, Ahmad N, Hamid S, Hamid S. Characterization of PLGA-PEG catharanthus roseus nanoparticles and assessing its anticancer effects in HER2-overexpressed breast cancer cells. Pharmacognosy Magazine. 2022; 18(78): 273-80.

38. Pham HNT, Vuong QV, Bowyer MC, Scarlett CJ. Phytochemicals derived from catharanthus roseus and their health benefits. Technologies. 2020; 8(4): 80.

39. Nayila I, Sharif S, Shahzad Lodhi M, Ur Rehman MF, Aman F. Synthesis, characterization and anti-breast cancer potential of an incensole acetate nanoemulsion from Catharanthus roseus essential oil; in silico, in vitro, and in vivo study. RSC Advances. 2023; 13(46): 32335-62.

40. Shofiyah A, Djati MS, Rifa'i M. Expression of IL-6 on breast cancer mice treated by combination of phyllanthus urinaria and catharanthus roseus extract. Biotropika: Journal of Tropical Biology. 2022; 10(2): 105-10.

41. Shofiyah A, Djati MS, Rifa'i M. Expression of IL-17 on breast cancer mice treated by combination of phyllanthus urinaria and catharanthus roseus extract. The Journal of Experimental Life Science. 2022; 12(2): 68-74.

42. Ozan Ç. Kuzey Kıbrıs'ta kullanılan tıbbi bitkiler [Yüksek Lisans Tezi]. Yakın Doğu Üniversitesi; 2011.

43. Dahmani W, Elaouni N, Abousalim A, Akissi ZLE, Legssyer A, Ziyyat A, et al. Exploring carob (Ceratonia siliqua L.): a comprehensive assessment of its characteristics, ethnomedicinal uses, phytochemical aspects, and pharmacological activities. Plants. 2023; 12(18): 3303.

44. Gregoriou G, Neophytou CM, Vasincu A, Gregoriou Y, Hadjipakkou H, Pinakoulaki E, et al. Anti-cancer activity and phenolic content of extracts derived from cypriot carob (Ceratonia siliqua L.) pods using different solvents. Molecules. 2021; 26(16): 5017.

45. Ghanemi FZ, Belarbi M. Phytochemistry and pharmacology of ceratonia siliqua L. leaves. Journal of Natural Product Research and Applications. 2021; 1(01): 69-82.

46. Dulce-María DA, Adrián CR, Cuauhtémoc RM, Ada-Keila MN, Jorge MC, Erika AS, et al. Isoflavones from black chickpea (Cicer arietinum L) sprouts with antioxidant and antiproliferative activity. Saudi Journal of Biological Sciences. 2021; 28(1): 1141-6.

47. Zakłos-Szyda M, Gałązka-Czarnecka I, Grzelczyk J, Budryn G. Cicer arietinum L. Sprouts' influence on mineralization of Saos-2 and migration of MCF-7 cells. Molecules. 2020; 25(19): 4490.

48. Namiranian P, Mardi R, Fadaei F, Sadati Lamardi SN, Tabarrai M. Nutritional recommendations for breast cancer treatment: a review of persian and conventional medicine resources. Asian Journal of Traditional, Complementary and Alternative Medicines [Internet]. 2021; 4. Available from: https://doi.org/10.22040/atcam.2021.270044.1017

49. Hassan H, Sayed AA. Anti-tumor effect of cicer arietinum against the triple-negative breast cancer cells. Egyptian Academic Journal of Biological Sciences, B Zoology. 2019; 11(2): 31-41.

50. Banjo TT, Aina YO, Falade FA. Phytopharmacotherapeutic and antimicrobial attributes of bitter apple (citrullus colocynthis)-a review. Covenant Journal of Physical and Life Sciences [Internet]. 2021 Aug 4 [cited 2024 May 9]; Available from: https://journals.covenantuniversity.edu.ng/index.php/cjpls/article/view/2655

51. Rasool S, Tayyeb A, Raza MA, Ashfaq H, Perveen S, Kanwal Z, et al. Citrullus colocynthis-mediated green synthesis of silver nanoparticles and their antiproliferative action against breast cancer cells and bactericidal roles against human pathogens. Nanomaterials (Basel). 2022; 12(21): 3781.

52. Li QY, Munawar M, Saeed M, Shen JQ, Khan MS, Noreen S, et al. Citrullus colocynthis (L.) schrad (bitter apple fruit): promising traditional uses, pharmacological effects, aspects, and potential applications. Front Pharmacol. 2022; 12: 791049.

53. Kafshgari HS, Yazdanian M, Ranjbar R, Tahmasebi E, Mirsaeed SRG, Tebyanian H, et al. The effect of citrullus colocynthis extracts on streptococcus mutans, candida albicans, normal gingival fibroblast and breast cancer cells. Journal of Biological Research - Bollettino della Società Italiana di Biologia Sperimentale [Internet]. 2019 Jun 21 [cited 2023 Dec 19];92(1). Available from: https://pagepressjournals.org/index.php/jbr/article/view/8201

54. Perveen S, Ashfaq H, Ambreen S, Ashfaq I, Kanwal Z, Tayyeb A. Methanolic extract of Citrullus colocynthis suppresses growth and proliferation of breast cancer cells through regulation of cell cycle. Saudi J Biol Sci. 2021; 28(1): 879-86.

55. Mandour YM, Refaat E, Hassanein HD. Anticancer activity, phytochemical investigation and molecular docking insights of Citrullus colocynthis (L.) fruits. Sci Rep. 2023; 13(1): 20038.

56. Shaikh IA, Alshabi AM, Alkahtani SA, Orabi MAA, Abdel-Wahab BA, Walbi IA, et al. Apoptotic cell death via activation of DNA degradation, Caspase-3 Activity, and suppression of Bcl-2 activity: an evidence-based citrullus colocynthis cytotoxicity mechanism toward MCF-7 and A549 cancer cell lines. Separations. 2022; 9(12): 411.

57. Abdulridha MK, Al-Marzoqi AH, Ghasemian A. The anticancer efficiency of citrullus colocynthis toward the colorectal cancer therapy. J Gastrointest Cancer. 2020; 51(2): 439-44.

58. Bharath R, Priya AJ, Jayaraman S, Devi RG. Induction of bax and activation of caspases by hydro ethanolic leaf extract of citrullus colocynthis (L)-mediated Apoptosis in breast cancer cell line (MCF-7). JPRI. 2021; 173-80.

59. Perveen S, Ashfaq H, Shahjahan M, Manzoor A, Tayyeb A. Citrullus colocynthis regulates de novo lipid biosynthesis in human breast cancer cells. J Cancer Res Ther. 2020; 16(6): 1294-301.

60. AlGhalban FM, Khan AA, Khattak MNK. Comparative anticancer activities of Ficus carica and Ficus salicifolia latex in MDA-MB-231 cells. Saudi J Biol Sci. 2021; 28(6): 3225-34.

61. Abdel-Rahman R, Ghoneimy E, Abdel-Wahab A, Eldeeb N, Salem M, Salama E, et al. The therapeutic effects of Ficus carica extract as antioxidant and anticancer agent. South African Journal of Botany. 2021; 141: 273-7.

62. Zhang Y, Wan Y, Huo B, Li B, Jin Y, Hu X. Extracts and components of Ficus carica leaves suppress survival, cell cycle, and migration of triple-negative breast cancer MDA-MB-231 cells. OncoTargets and Therapy. 2018; 11: 4377-86.

63. Alsubhi NH. The use of medicinal plants for combating breast cancer: a comprehensive review. Journal of Experimental Biology and Agricultural Sciences. 2023; 11(1): 24-40.

64. Ghandehari F, Fatemi M. The effect of Ficus carica latex on 7, 12-dimethylbenz (a) anthracene-induced breast cancer in rats. Avicenna J Phytomed. 2018; 8(4): 286-95.

65. Sánchez-Valdeolívar CA, Alvarez-Fitz P, Zacapala-Gómez AE, Acevedo-Quiroz M, Cayetano-Salazar L, Olea-Flores M, et al. Phytochemical profile and antiproliferative effect of Ficus crocata extracts on triple-negative breast cancer cells. BMC Complementary Medicine and Therapies. 2020; 20(1): 191.

66. Nazmi SA, Nourazarian A, Bahhaj R, Khakikhatibi F. The anticancer effect of arctium lappa and glycyrrhiza glabra on HT-29 colon cancer and MCF-7 Breast Cancer Cell Lines. 2018; 5(2): 133-7.

67. Ahmed OH, Kadhim E jawad, Tawfeeq AA, Jabir MS. Review of the usage of medicinal herbs in the treatment of cancer. Journal of Survey in Fisheries Sciences. 2023; 10: 3124-34.

68. Hamad GM, I. Abd Elaziz A, A. Hassan S, Aly Shalaby M, Abdelrazek Abdel Azim Mohdaly A. Chemical composition, antioxidant, antimicrobial and anticancer activities of licorice (Glycyrrhiza glabra L.) Root and Its Application in Functional Yoghurt. JFNR. 2020; 8(12): 707-15.

69. Hajirahimkhan A, Howell C, Bartom ET, Dong H, Lantvit DD, Xuei X, et al. Breast cancer prevention with liquiritigenin from licorice through the inhibition of aromatase and protein biosynthesis in high-risk women's breast tissue. Sci Rep. 2023; 13(1): 8734.

70. Ibrahim MG, El-Senduny FF, Youssef MM, Elimam DM, Bar FMA, Badria FA. Acetyl glycyrrhetinic acid methyl ester as a promising glycyrrhizin derivative against the breast cancer cells (MCF-7). Journal of Reports in Pharmaceutical Sciences. 2019; 8(2): 161.

71. He L, Wang X, Ma Q, Zhao W, Jia Y, Dong G, et al. Glycyrrhizin inhibits the invasion and metastasis of breast cancer cells via upregulation of expressions of miR-200c and e-cadherin. Tropical Journal of Pharmaceutical Research. 2020; 19(9): 1807-13.

72. Tuli HS, Garg VK, Mehta JK, Kaur G, Mohapatra RK, Dhama K, et al. Licorice (Glycyrrhiza glabra L.)-derived phytochemicals target multiple signaling pathways to confer oncopreventive and oncotherapeutic effects. Onco Targets Ther. 2022; 15: 1419-48.

73. Poustforoosh A, Faramarz S, Negahdaripour M, Tüzün B, Hashemipour H. Tracing the pathways and mechanisms involved in the anti-breast cancer activity of glycyrrhizin using bioinformatics tools and computational methods. Journal of Biomolecular Structure and Dynamics. 2024; 42(2): 819-33.

74. Akhil G, Kariyil B, Akshatha GD, Bhatt SV, Dhanusha G, John R. Germinated seeds of Hordeum vulgare target extrinsic pathway of apoptosis in triple-negative breast cancer cells. Pharmacognosy Magazine. 2020; 16(05): 531–9.

75. Itou J, Nakamura A, Hokazono H, Toi M. Supplementation with fermented barley extract prevents mammary epithelial cell invasion in an early breast cancer model. Acta Histochem Cytochem. 2021; 54(2): 73-8.

76. Xie M, Liu J, Tsao R, Wang Z, Sun B, Wang J. Whole grain consumption for the prevention and treatment of breast cancer. Nutrients. 2019; 11(8): 1769.

77. Abuderman AA, Syed R, Alyousef AA, Alqahtani MS, Ola MS, Malik A. Green synthesized silver nanoparticles of myrtus communis L (AgMC) extract inhibits cancer hallmarks via targeting aldose reductase (AR) and associated signaling network. Processes. 2019; 7(11): 860.

78. Harassi Y, Tilaoui M, Idir A, Frédéric J, Baudino S, Ajouaoi S, et al. Phytochemical analysis, cytotoxic and antioxidant activities of Myrtus communis essential oil from Morocco. J Complement Integr Med. 2019; 16(3): /j/jcim.2019.16.issue-3/jcim-2018-0100/jcim-2018-0100.xml.

79. Kasikci Y, Kasikci Y, Pazarbasi A, Karacay S, Kaya D, Duran G, Kumar A, et al. Medicinal & aromatic plants induction of tumor-selective cytotoxicity by myrtus communis L. extract and its bioactive metabolite 1, 8-cineole. 2021. Medicinal and Aromatic Plants Research Journals. 2021; 10: 371.

80. Paparella A, Shaltiel-Harpaza L, Ibdah M. β-Ionone: its occurrence and biological function and metabolic engineering. Plants (Basel). 2021; 10(4): 754.

81. Simkin AJ. Carotenoids and apocarotenoids in planta: their role in plant development, contribution to the flavour and aroma of fruits and flowers, and their nutraceutical benefits. Plants (Basel). 2021; 10(11): 2321.

82. Bumidin MS, Johari FA, Risan NF, Nasir MHM. The effect of aqueous extracts of nigella sativa on breast cancer cell line Mcf-7: an in vitro study. Science Heritage Journal (GWS). 2018; 2(1): 13-7.

83. Khurshid Y, Syed B, Simjee SU, Beg O, Ahmed A. Antiproliferative and apoptotic effects of proteins from black seeds (Nigella sativa) on human breast MCF-7 cancer cell line. BMC Complement Med Ther. 2020; 20(1): 5.

84. Das S, Ghosh A, Upadhyay P, Sarker S, Bhattacharjee M, Gupta P, et al. A mechanistic insight into the potential anti-cancerous property of Nigella sativa on breast cancer through micro-RNA regulation: an in vitro & in vivo study. Fitoterapia. 2023; 169: 105601.

85. Pandey M. Medicinal plants for prevention and cure of breast cancer: a review. IJSR. 2022; 1: 54-8.

86. Sadwal S, Kaur S, Aniqua A. Medicinal plants in combating breast carcinogenesis: a review on recent investigations. J Cancer Oncol. 2022; 6(2): 000182.

87. Rashed K. Phytocontent and biological effects of olea europaea L. : a review. Plantae Scientia. 2022; 5(2): 36-44.

88. Antoniou C, Hull J. The anti-cancer effect of olea europaea L. Products: a review. Curr Nutr Rep. 2021; 10(1): 99-124.

89. Elamin MH, Elmahi AB, Daghestani MH, Al-Olayan EM, Al-Ajmi RA, Alkhuriji AF, et al. Synergistic anti-breast-cancer effects of combined treatment with oleuropein and doxorubicin in vivo. Altern Ther Health Med. 2019; 25(3): 17-24.

90. Mansouri N, Alivand MR, Bayat S, Khaniani MS, Derakhshan SM. The hopeful anticancer role of oleuropein in breast cancer through histone deacetylase modulation. Journal of Cellular Biochemistry. 2019; 120(10): 17042-9.

91. Moral R, Escrich E. Influence of olive oil and its components on breast cancer: molecular mechanisms. Molecules. 2022; 27(2): 477.

92. Daghestani M, Rashed SAA, Bukhari W, Al-Ojayan B, Ibrahim EM, Al-Qahtani AM, et al. Bactericidal and cytotoxic properties of green synthesized nanosilver using Rosmarinus officinalis leaves. Green Processing and Synthesis. 2020; 9(1): 230-6.

93. Lamponi S, Baratto MC, Miraldi E, Baini G, Biagi M. Chemical profile, antioxidant, anti-proliferative, anticoagulant and mutagenic effects of a hydroalcoholic extract of tuscan rosmarinus officinalis. Plants. 2021; 10(1): 97.

94. Andrade JM, Faustino C, Garcia C, Ladeiras D, Reis CP, Rijo P. Rosmarinus officinalis L.: an update review of its phytochemistry and biological activity. Future Sci OA. 2018; 4(4): FSO283.

95. Tabatabaei SM, Kianinodeh F, Nasiri M, Tightiz N, Asadipour M, Gohari M. In vitro inhibition of MCF-7 human breast cancer cells by essential oils of rosmarinus officinalis, thymus vulgaris L., and lavender X intermedia. Arch Breast Cancer. 2018; 5: 81-9.

96. Ijaz S, Iqbal J, Abbasi BA, Ullah Z, Yaseen T, Kanwal S, et al. Rosmarinic acid and its derivatives: current insights on anticancer potential and other biomedical applications. Biomed Pharmacother. 2023; 162: 114687.

97. Doagooyan M, Ghanbari Hassan Kiadeh S, Boustan A. Breast cancer; overview and presented silymarin as well- potential as a treatment. 2022.

98. Doagooyan M, Alavizadeh SH, Sahebkar A, Houshangi K, Khoddamipour Z, Gheybi F. Anti-tumor activity of silymarin nanoliposomes in combination with iron: in vitro and in vivo study. Int J Pharm X. 2023; 6: 100214.

99. Šimora V, Ďúranová H, Bilcikova J, Habán M. Milk thistle (silybum marianum): a valuable medicinal plant with several therapeutic purposes. Journal of Microbiology Biotechnology and Food Sciences. 2020; 9.

100. Choe Choe U, Whent M, Luo Y, et al. Total phenolic content, free radical scavenging capacity, and anti-cancer activity of silymarin. Journal of Food Bioactives. 2020; 10: 53-63.

101. Delmas D, Xiao J, Vejux A, Aires V. Silymarin and cancer: a dual strategy in both in chemoprevention and chemosensitivity. Molecules. 2020; 25(9): 2009.

102. Ramedani A, Sabzevari O, Simchi A. Processing of liposome-encapsulated natural herbs derived from Silybum marianum plants for the treatment of breast cancer cells. Scientia Iranica. 2022; 29(6); 3619-27.