Chapter

Cytotoxic Activity of Essential Oils of Some Species from Lamiaceae Family

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Abstract

Cancer is considered one of the most lethal diseases in the world, with a prevalence of 439.2 cases and 163.5 deaths per 100,000 inhabitants, in the period from 2011 to 2015; this disease has a greater impact in underdeveloped countries. For the treatment of this disease, a combination of chemotherapy with surgery or radiation is generally used, however, it is not exempt from adverse effects or resistance of the tumor to this type of treatment, for this reason the search for new treatments is constant. The plants are a possible source to achieve this; Lamiaceae is a family of plants widely distributed on the planet and has been used traditionally for the treatment of different diseases, and various essential oils with the potential for cancer treatment have been isolated from this species. The scope of this review is to present 46 essential oils isolated from different species of Lamiaceae which have been tested against different cancer cell lines.

Keywords: essential oils, Lamiaceae family, cytotoxic activity

1. Introduction

Cancer is a complex disease due to its multiple etiologies, and cancer cells are different to normal cells in many ways. The main characteristics of cancer cells are the cell growth out-of-control in a part of the body that spreads to surrounding tissue, and cancer cells are less specialized than the normal cells. Cancer cells ignore signals that normally tell cells to stop dividing or that begin the process of apoptosis. Also, these cells frequently evade the immune system.

These cells influence the normal cells, molecules, and blood vessels which feed tumors supplying with oxygen and nutrients, which they need to grow. These blood vessels also remove waste products from tumors [1].

Cancer has a large global impact; between 2011 and 2015, the number of new cases of cancer was 439.2 per 100,000 habitants, the cancer mortality rate was 163.5 per 100,000, and cancer mortality was higher for men than women [2].

In 2012, approximately 57% of new cancer cases were detected in less developed countries such as those in Central America and some parts of Africa and Asia,

where 65% of cancer deaths occurred. In 2030, it is expected that the number of new cancer cases will rise to 23.6 million [2].

In 2017, it was estimated that in the USA, national expenditures for cancer care were $147.3 billion dollars, and the cost will rise with the increase in cancer prevalence and population age.

Currently, many types of cancer treatment are used. Most patients with cancer undergo a combination of treatments, such as surgery with chemotherapy, radiation, immunotherapy, targeted therapy, or hormone therapy. Chemotherapy is one of the most common cancer treatments, but the drugs used produce severe side effects, such as nausea, vomiting, and alopecia, among others, which diminish the quality of life of the patients.

The use of plants in the treatment of many diseases is an ancient practice that has an increased use in recent years. Medicinal plants are a source of compounds with biological activities as anticancer agents, and over 50% of the drugs used in the clinical treatment of cancer, such as Taxol, camptothecin, vincristine, and vinblastine, were obtained from natural sources.

Essential oils (EOs) are a highly complex, volatile, and odorous mixture. The main components are monoterpenes, sesquiterpenes, and aromatic compounds. EOs are obtained mainly by steam distillation [3]. EOs have several activities, such as antimicrobial, anti-inflammatory, bactericidal, antiviral, fungicidal, antiangiogenic, and antitumor activities [4].

The Lamiaceae family comprises 240 genera and 7200 species distributed around the world. Most members of this family are perennial or annual herbs with square stems and are woody shrubs or subshrubs. This family is characterized by aromatic plants, which are widely used as culinary herbs, such as basil, mint, oregano, and sage. Species of this family are important ornamental and medicinal plants and are considered one of the most important sources of EOs of economic importance. In fact, different studies suggest that several EOs obtained from this family have demonstrated cytotoxic activity against different cell cancer lines and could be used as a preventive and alternative treatment for cancer [5]. Several EOs obtained from plants of this family contain high amounts of monoterpenes, such as thymol, carvacrol, 1,8-cineole, and limonene, among others, and the cytotoxic activity of some of these compounds has been studied.

The aim of this review is to provide a critical overview of the research on the traditional medicine basis, cytotoxic properties, cancer cell lines targeted, and composition of EOs isolated from plants belonging to the Lamiaceae family.

2. *Satureja*

Satureja L., which includes approximately 38 species in the Mediterranean region, is used in folk medicine to treat various ailments, such as cramps, muscle pains, nausea, indigestion, diarrhea, and infectious diseases, as well as for its antioxidant, cytotoxic, antidiabetes, anti-HIV, antihyperlipidemic, reproduction-stimulating, expectorant, and vasodilatory effects.

S. cilicica P.H. Davis is an endemic species of Turkey. EO from aerial parts of *S. cilicica* collected in Turkey was obtained in a yield of 0.69% v/w. The main identified compounds were *p*-cymene (17.68%), carvacrol (14.02%), γ-terpinene (11.23%), and thymol (8.76%). The cytotoxic activity of the EO was determined in the MCF-7 (breast cancer) cell line, revealing an IC_{50} value of 268 μg/mL [6].

S. sahandica Bornm. aerial parts were collected in Iran. The EO yield was 0.52% (w/w). Thymol (40%), γ-terpinene (28%), and ρ-cymene (22%) were the main

compounds. The cytotoxicity of the EO in MCF-7, Vero, SW480 (adenocarcinoma cell), and JET 3 (choriocarcinoma cells) cell lines was dose-dependent, with IC_{50} values of 15.6, 15.6, 125, and 250 μg/mL, respectively [7].

S. intermedia L. is used to treat diarrhea, nausea, cramps, muscle pain, indigestion, and infectious diseases. A sample was collected in Iran, and the major components were thymol (34.5%), γ-terpinene (18.2%), and *p*-cymene (10.5%). The cytotoxic activity was tested in the 5637 (urinary bladder carcinoma) and KYSE (human Asian squamous cell carcinoma) cell lines, and an IC_{50} value of 156 μg/mL was obtained in both cases [8].

S. intermedia C.A. Mey EO was obtained from the aerial parts collected in Fars Province, Iran. The main components of the EO were γ-terpinene (37.1%), thymol (30.2%), p-cymene (16.2%), limonene (3.9%), α-terpinene (3.3%), and myrcene (2.5%). The EO showed an $IC_{50} \geq 50$ μg/mL in the Hep-G2 (hepatocellular carcinoma) and MCF-7 cell lines. The effect was evaluated by the crystal violet staining method [9].

S. khuzistanica Jamzad is used as analgesic and antiseptic in Iran. The aerial parts were collected in southern Iran. The EO was analyzed by GC/FID and GC/MS. The EO yield was 0.42% (w/w), and the main component was carvacrol (92.87%). MTT cytotoxicity assay was employed. The EO reduced the viability of Vero, SW480 (colon adenocarcinoma), MCF-7, and JET 3 cell lines, with IC_{50} values of 31.2, 62.5, 125, and 125 μg/mL, respectively [10].

S. montana subsp. *pisidica* L. is used for its antiseptic, aromatic, carminative, digestive, and expectorant properties and in the treatment of insect bites. The major compounds of the EOs obtained from the aerial parts collected in Korab and Galicica were carvacrol, thymol, carvacrol methyl ether, and β-linalool. The cytotoxic effect of the EOs was tested against MDA-MB-361, MDA-MB-453 (human mammary metastatic carcinoma), HeLa, LS174 (human colorectal adenocarcinoma), and MRC5 (fibroblast of lung cells) cell lines. The EO from Korab had higher activity than the oil from Galicica, particularly against the HeLa and MDA-MB-453 cell lines, with IC_{50} values of 63.5 and 72.3 μg/mL, respectively [11].

S. bakhtiarica Bunge. is traditionally used for its antiseptic, carminative, stimulant, diaphoretic, diuretic, anesthetic, antispasmodic, analgesic, antioxidant, sedative, and antimicrobial properties. *S. bakhtiarica* is an endemic plant in the southern region of Iran. Leaves of *S. bakhtiarica* were collected in the Fars Province of Iran. The chemical composition of the EO was determined by GC/MS, and the main components were phenol (56.35%), thymol (13.82%), p-cymene (8.79%), and carvacrol (2.88%). An MTT cytotoxicity assay was used to test the effect of the EO on HEK (human normal embryonic kidney cells), MDA-MB-231, and SKOV3 (human ovary cancer cells) cell lines. The EO showed antitumor activity against the SKOV3 and MDA-MB-231 cell lines (IC_{50} values of 74.6 μg/mL and IC_{50} of 83.7 μg/mL, respectively) [12].

3. *Nepeta*

N. schiraziana Boiss possesses medicinal properties such as antitussive, diaphoretic, antispasmodic, antiasthmatic, diuretic, emmenagogue, and antipyretic effects. The aerial parts of *N. schiraziana* were collected in Iran. The compounds identified in the EO were 1,8-cineole (33.67%), germacrene D (11.45%), β-caryophyllene (9.88%), caryophyllene oxide (7.34%), *α*-pinene (4.59%), and camphor (3.75%). The EO was tested against Hep-G2 (IC_{50} of 85.74 μg/mL) and MCF-7 (IC_{50} of 32.56 μg/mL) cell lines [13].

N. rtanjensis Diklić & Milojević is found only in a few localities of Mt. Rtanj in northeast Serbia. This plant has antibacterial, antifungal, allelopathic, and phytotoxic activities. *N. rtanjensis* was cultivated at the University of Belgrade, Serbia. Chemical analysis revealed that *N. rtanjensis* EO contains *trans*,*cis*-nepetalactone (71.66%), *cis*,*trans*-nepetalactone (17.21%), α-pinene (3.28%), 2-methoxy-para-cresol (1.85%), and α-copaene (0.86%). Cytotoxic assays were performed on five tumor cell lines (HeLa, A549, lung adenocarcinoma cells; LS-174, human colon cancer cells; K562, human myelogenous leukemia cells; and MDA-MB-231), and the IC_{50} values were 0.050, 0.064, 0.097, 0.052, and 0.097 μL/mL, respectively [14].

N. sintenisii Bornm. The EO is used in Iranian folk medicine as a diuretic, antitussive, and antispasmodic treatment. The plant was collected in Neyshabur, Khorasan-Razavi, Iran. The yield of EO was 0.5% v/w, and the composition was determined by using GC/MS. The major compounds were 4aα,7α,7aβ-nepetalactone (51.74%), β-farnesene (12.26), 4aα,7α,7aα-nepetalactone (8.01%), germacrene D (5.01%), and 4α,7α,7aα-nepetelactone (3.71%). The cytotoxicity was evaluated against four cell lines, A2780, HeLa, LS180, and MCF-7. The IC_{50} values were 51.98, 20.37, 42.64, and 43.75 μg/mL, respectively [15].

N. menthoides Boiss & Buhse is an herbaceous aromatic plant endemic to northwest Iran and has been used to treat gastrodynia, insomnia, high blood pressure, bone pain, and rheumatism. The aerial parts were collected in Ardabil, Iran. The EO was analyzed by GC/MS. The major components were 4a-α,7β,7a-α-nepetalactone (18.39%), 4a-α,7α,7a-α-nepetalactone (17.57%), 1,8-cineol (16.66%), and geranyl acetate (7.0%). The cytotoxic activity was evaluated against HT-29 (colon carcinoma), Caco-2 (colorectal adenocarcinoma), T47D (breast ductal carcinoma), and NIH-3 T3 cell lines using the MTT method. The IC_{50} values were 30.7, 19.37, and 32.24 μg/mL, respectively [16].

4. *Thymus*

The genus *Thymus* consists of approximately 215 species distributed throughout Europe, Asia, and North Africa. Most of these plants are important in food, pharmaceutical, and cosmetic fields. Many species have been investigated for their preservative effects on foods, protecting the food from lipid peroxidation. In traditional medicine, the leaves and flowering aerial parts of *Thymus* species have been used extensively for their tonic, antiseptic, antitussive, and carminative properties in the treatment of colds, coughs, sore throats, cystitis, insomnia, bronchitis, and indigestion.

T. munbyanus Boiss. & Reut. is an endemic species of North Africa and is used as an antimicrobial, antioxidant, and antiproliferative agent. Fresh aerial parts of *T. munbyanus* were collected in Hennaya, Algeria. The EO was analyzed by GC and GC/MS. The main components of the oil were carvacrol (71%), *p*-cymene (8.3%), and ϒ-terpinene (5.9%). The *T. munbyanus* EO showed antiproliferative activity against the human acute monocytic leukemia cell line (THP-1, 100 μg/mL) using MTT assay [17].

T. munbyanus subsp. *coloratus* Boiss. and Reut. has been reported to be effective against cough, colds, influenza, sore throat, abdominal bloating, and endocrine gland diseases and as a depurative agent. Inflorescences and vegetative parts (stems + leaves) of *T. munbyanus* subsp. *coloratus* collected in Algeria yielded 0.2% and 0.1% w/w EO, respectively. The principal components of the EO from flowers were borneol (44.8%), camphor (5.7%), 1,8-cineole (6.0%), and germacrene D (5.0%). The major constituents of the EO from aerial parts were borneol (31.2%), camphor (13.6%), and camphene (7.5%). The cytotoxic activity was tested, and the EO from flowers showed higher activity against the A375 (IC_{50} of 46.95 μg/mL), T98G (human glioblastoma multiforme; IC_{50} of 51.54 μg/mL), and MDA-MB-231 (IC_{50} of 97.27 μg/mL) cell lines than that from leaves and stems. The EO from leaves and

stems was cytotoxic against T98G (IC_{50} of 91.83 μg/mL), MDA-MB-231 (IC_{50} of 84.77 μg/mL), and A375 (IC_{50} > 100 μg/mL) cell lines [18].

T. carmanicus Jalas is used in Iranian folk medicine in the treatment of rheumatism and skin disorders and as an antibacterial agent. Aerial parts were collected from Iran, and the EO was obtained in 2.67% w/w yield. The main components were carvacrol (51.0%), thymol (20.84%), borneol (6.80%), cymene (6.25%), γ-terpinene (5.50%), and β-myrcene (1.63%). The IC_{50} value was 0.44 μL/mL in KB cell line (oral carcinoma) [19].

T. vulgaris L. is reported to have antiseptic, antispasmodic, antimicrobial, antioxidant, anti-inflammatory, and anticancer effects. This plant was cultivated in Helwan University Cairo/Egypt. EO was obtained from the fresh and aerial parts with a yield of 0.21% v/w. The major constituents were p-cymene (31.62% v/w), γ-terpenine (17.72% v/w), thymyl methyl ether (9.83% v/w), and thymol (7.38% v/w). The cytotoxic effect of EO was tested in four cell lines: A-549, IC_{50} of 7.22 μg/mL; HCT-116, IC_{50} of 3.61 μg/mL; CaCo-2, IC_{50} of 1.93 μg/mL; and MCF-7, IC_{50} of 9.52 μg/mL [20].

5. *Mentha*

The genus *Mentha* includes 20 species found all over the world. Most *Mentha* species are perennial, contain essential oils, and are widely cultivated as industrial crops for essential oil production. Many EO chemotypes have a distinct aromatic flavor conferred by different terpene. The whole herb of these species has been used to extract many compounds that have been evaluated as antifungal, antiviral, antimicrobial, insecticidal, antioxidant, antiamoebic, antihemolytic, antiallergenic, and antitumoral agents.

M. spicata L. is a medicinal plant, and its EO inhibits free radical reactions, retards the oxidative rancidity of lipids, and shows antimicrobial and antitumor activities. The major compounds in the EO from *M. spicata* collected in China were carvone (65.33%), limonene (18.19%), dihydrocarvone (2.97%), and camphene (2.34%). The cytotoxicity was evaluated in a HeLa cell line, and an IC_{50} value of approximately 2.08 μg/mL was obtained [21].

M. piperita L. is commonly known as peppermint. It is widely grown in temperate areas of the world, particularly Europe, North America, and North Africa. The EO extracted from its aerial parts was analyzed by GC/MS, and the main component was menthol (47.5%). The cytotoxic activity of the EO was tested against HeLa, A549, and MRC-5 (human fibroblast lung cells) using MTT assay. The IC_{50} values were 165.24, 183.00, and 197.08 μg/mL, respectively. EO was obtained from *M. piperita* collected in Guatemala in a yield of 0.50% w/w. The IC_{50} values of the EO against the AGS, A375, and A431 cell lines were 0.35, 0.40, and 0.23 μL/mL, respectively [22].

M. pulegium L. is commonly known as pennyroyal. This plant is traditionally used in the treatment of infectious diseases. Analysis of the EO by GC/MS revealed pulegone (68.7%) as the main component. The cytotoxic activity of the EO was tested against HeLa, A549, and MRC-5 cell lines using MTT assay. The IC_{50} values of the EO were 168.58, 253.64, and 189.48 μg/mL, respectively [23].

6. *Ocimum*

The genus *Ocimum* includes approximately 150 species, comprising annual and perennial herbs and shrubs native to the tropical and subtropical regions of Asia, Africa, and Central and South America. *Ocimum* species are commercially cultivated aromatic crops in India and other countries for the EO and high-value

aromatic chemicals used extensively in food, perfumery, cosmetic and pharmaceutical preparations, and as spices. *Ocimum* species are known for their diverse use in folk medicine for the treatment of various gastric and urinary diseases, insomnia, inflammation, and constipation due to their diverse biological actions, such as carminative, stimulant, antiseptic, antimicrobial, antioxidant, antipyretic, insecticidal, and antispasmodic activities.

Ocimum basilicum L. grows in several regions all over the world and is traditionally used to treat anxiousness, grippe, infectious diseases, headaches, coughs, acne, diarrhea, constipation, warts, worms, and kidney malfunction. EO from its leaves has insecticidal, pesticidal, antibacterial, antioxidant, antiviral, antifungal, antiulcer, cytotoxic, and larvicidal activities.

Plants were collected in Guatemala, and the yield of EO was 0.33% w/w. The main components of the EO were methyl cinnamate (70.1%), linalool (17.5%), β-elemene (2.6%), and camphor (1.52%). The IC_{50} values of the EO against AGS (epithelial gastric adenocarcinoma), A375 (epithelial malignant melanoma), and A431 (epithelial squamous carcinoma) cell lines were 0.39, 0.36, and 0.34 μL/mL, respectively [22].

This oil was also tested against HeLa (cervical adenocarcinoma cells; IC_{50} of 90.5 μg/mL) and HEp-2 (human epithelioma; IC_{50} of 96.3 μg/mL) cell lines [24]. In *O basilicum* L. collected in Egypt (yield of 0.85% v/w), the major components were estragole (75.45%), 1,8-cineole (7.56%), linalool (5.01%), trans-anethole (3.72%), and methyleugenol (3.48%). The anticancer activity was assessed in HL-60 (promyelocytic leukemia) and NB4 (acute promyelocytic leukemia) cell lines. The EO was tested at doses of 200 μg/mL in both cell lines and killed 82.33% of HL-60 cells and 73.38% of NB4 cells [25].

O. canum Sims. is used in traditional Indian medicinal for treating diabetes, cold, fever, inflammation, and headaches. The EO was obtained from its leaves. The main components were camphor (39.77%), naphtalene (7.37%), valencene (5.80%), α-pinene (5.59%), camphene (5.20%), and caryophyllene (5.62%). The cytotoxic activity of the EO was tested against MCF-7 cells (IC_{50} of 60 μg/mL) [26].

O. kilimandscharicum Guerke, popularly known as "Basil African blue," is a semi-evergreen shrub native to East Africa and used in traditional medicine for the treatment of constipation, abdominal pain, cough, and diarrhea. The chemical composition of the EO was determined by GC/MS, and the main components were camphor (51.81%), 1,8-cineole (20.13%), and limonene (11.23%). The EO was evaluated against OVCAR-03 cell line (human epithelial ovarian adenocarcinoma) using a sulforhodamine B (SRB) colorimetric assay, with an IC_{50} of 31.90 μg/mL [27].

7. *Salvia*

The Salvia genus comprises more than 960 species, which are known as Sage in folk medicine and have been used in the treatment of different ailments, such as stomach pain, diarrhea, fever, inflammation, headaches, bruises, and sprains.

Aerial parts of these plants usually contain flavonoids, triterpenoids, and essential oils. Diterpenoids are the main compounds in the roots. These compounds show a variety of activities, and different pharmacological models have been used to explain their mechanisms of activity.

S. officinalis L. is used in traditional medicine to treat microbial infections, cancer, malaria, and inflammation and to disinfect homes after sickness. This plant was collected in south-central Italy in 2008–2009. The leaves were used to obtain an EO, the composition of which was determined by GC/MS, with a yield of 0.55–2.2% on a dry mass basis. The main components were α-thujone, camphor, borneol,

γ-muurolene, and sclareol. The anticancer activity was tested in the cell lines M14, A375, and A2058. The IC_{50} values were 8.2, 12.1, and 11.7 μg/mL, respectively [28].

S. macrosiphon Boiss is used for treating infection; rheumatoid arthritis; chronic pain; inflammatory, cardiovascular, and cerebrovascular diseases; and as an antioxidant, acetylcholinesterase-inhibiting, antinociceptive, anti-inflammatory, antidepressant, anxiolytic, antitumor, and cytotoxic agent. *S. macrosiphon* was collected in Iran. The aerial parts yielded 0.2% v/w of EO. Analysis of the EO showed that linalool (19%), β-cedrene (14.64%), and β-elemene (13.33%) were the major components. The effect of the EO on the proliferation of cell lines MCF-7, MDA-MB-231, and T47D was assessed, and the IC_{50} values were 0.155, 0.145, and 0.093 μg/mL, respectively [29].

S. lavandulifolia Vahl is a medicinal plant native to the Iberian Peninsula. It is used to treat gastric problems and inflammatory disorders. The composition of its EO was determined by GC/MS, and camphor (29.1%) was the main component. The cytotoxic activity of the EO was tested against HeLa, A549, and MRC-5 cell lines using MTT assay. The IC_{50} values of the EO were 133.56, 140.10, and 131.50 μg/mL, respectively [30].

8. *Lavandula*

The genus *Lavandula* includes more than 20 species, and the EOs from the species of this genus have been applied in food, pharmaceutical, and agricultural industries as biological products. Four medicinal plants of this genus (*L. vera* DC, *L. angustifolia* Miller, *L. latifolia* Medikus, and *L. hybrida* Rev) were collected in Italy. The EO constituents were analyzed, and the major compounds were as follows: linalool (36.15%), linalyl acetate (17.08%), and terpinen-4-ol (16.13%) in *L. vera* DC; linalool (56.57%) and camphor (10.01%) in *L. angustifolia* Miller; linalool (34.43%), linalyl acetate (24.36%), and camphor (8.84%) in *L. latifolia* Medikus; and linalool (39.24%), linalyl acetate (22.88%), and 1,8-cineole (6.74%) in *L. hybrida* Rev. The EOs were tested in Caco-2 cell line (epithelial colorectal adenocarcinoma), and the cytotoxic effect of EOs was very low [31].

L. angustifolia Mill. was collected in the southeastern region of Brazil. The yield obtained for its EO was 0.28% (w/w), and the major components were borneol (22.4%), epi-α-muurolol (13.4%), α-bisabolol (13.1%), precocene I (13%), and eucalyptol (7.9%). The cytotoxic activity was tested in the cell line GM07492-A and was observed only at a high concentration (IC_{50} of 243.7 μg/mL) [32].

L. angustifolia Mill was collected in Bulgaria. Analysis of the EO extracted from its aerial parts revealed linalool (40.3%) as the main component. The cytotoxic activity of the EO was tested against HeLa (IC_{50} of 80.62 μg/mL), A549 (88.90 of μg/mL), and MRC-5 (75.19 of μg/mL) cell lines using MTT assay [30].

9. *Origanum*

Origanum species are herbaceous perennial shrubs native to Europe and North Africa. These plants have aromatic leaves. This genus includes important culinary plants, such as marjoram and oregano.

O. onites Elmalı is used in Turkey as a condiment or aromatic tea, and a sample of this species was collected in Antalya, Turkey. EO was obtained from the herbal parts of the plant. The composition was determined by GC/MS; the main components were carvacrol (24.52%), thymol (15.66%), and linalool (50.53%).

The cytotoxicity of the EO, thymol, and carvacrol was determined against hepatoma G2 cells (Hep G2), and the IC_{50} values were 149.12, 53.09, and 60.1 μg/mL, respectively [33].

O. vulgare L. is used in traditional medicine for treating colds, indigestion, and upset stomach. The plant was collected in Guatemala, and the yield of EO was 0.66% w/w. The IC_{50} values of the EO against epithelial gastric adenocarcinoma, epithelial malignant melanoma, and epithelial squamous carcinoma were 0.18, 0.09, and 0.08 μL/mL, respectively [22].

O. vulgare L. is commonly known as oregano and *O. majorana* L. as sweet marjoram. The EOs from both species have antioxidant and antimicrobial properties; these plants were collected in Faisalabad, Pakistan, in July–August 2008. The EOs were analyzed by GC and GC/MS. The main components of the EO from *O. vulgare* were terpinen-4-ol (20.9%), linalool (15.7%), linalyl acetate (13.9%), limonene (13.4%), and α-terpineol (8.57%). The major compounds in the EO from *O. majorana* were thymol (21.6%), carvacrol (18.8%), and α-terpineol (8.57%).

The cytotoxic activity of the EO from *O. vulgare* was tested against MCF-7, prostate cancer (LNCaP), and NIH3T3 cell lines. The IC_{50} values were 70, 85.3, and 300.5 μg/mL, respectively. The IC_{50} values for the EO from *O. majorana* were 100, 90.1, and 320.3 μg/mL, respectively [34].

The EO obtained from *O. vulgare* collected in Córdoba, Argentina, was analyzed by GC/MS. Analysis of the chemical composition showed carvacrol and thymol as the predominant compounds. The cytotoxicity activity was evaluated in cultured A549 cells, and this oil reduced the viability of the cells (IC_{50} of 2.25 μg/mL) [35].

Tetradenia riparia Hochst Codd is used in traditional medicinal to treat cough, dropsy, diarrhea, fever, headaches, malaria, and toothaches. The main components of its EO were *E*,*E*-farnesol (15%), aromadendrene oxide (14.7%), and dronabinol (11%). The cytotoxic activity was tested against HT29 (IC_{50} of 6.93 μg/mL), MCF-7 (IC_{50} of 129.57 μg/mL), HeLa (IC_{50} of 155 μg/mL), HepG-2 (IC_{50} of 149.97 μg/mL), glioblastoma (M059; IC_{50} of 217.97 μg/mL), U343 (IC_{50} of 221.30 μg/mL), and U251 (IC_{50} of 109.90 μg/mL) cells using an XTT-based toxicology assay kit [36].

T. riparia leaves were collected in Umuarama, Brazil. 9β,13β-Epoxy-7-abietene (1) was isolated from the EO. The cytotoxic activities of the EO and (1) were determined by MTT assay in the MDA-MB-435, HCT-8, SF-295, and HL-60 cell lines. The EO and compound (1), at concentrations of 50 μg/mL and 25 μg/mL, respectively, showed high cytotoxic potential against the cell lines SF-295 (78.06% and 94.80%), HCT-8 (85.00% and 86.54%), and MDA-MB-435 (59.48% and 45.43%) [37].

Ajuga chamaepitys L. Schreb grows in the Mediterranean region and is used as a diuretic and emmenagogue. This plant was collected in Rocca Mattei, Italy, and the composition of the EO isolated from the aerial parts was determined by GC and GC/MS. Ethyl linoleate (13.7%), germacrene D (13.4%), kaurene (8.4%), β-pinene (6.8%), and phytol (5.3%) were the major components. The EO had moderate cytotoxic activity against the MDA-MB-231 cell line (IC_{50} of 36.88 μg/mL) and an IC_{50} value of 60.48 μg/mL against the human colon carcinoma cell line (HCT116) [38].

Ziziphora tenuior L. is used in Jordan for the treatment of stomachache, dysentery, and fever. The EO was obtained in 0.72% yield, and the composition was determined using GC/MS; pulegone (46.8%) and *p*-menth-3-en-8-ol (12.5%) were the major compounds. The EO was tested against HepG2 cell line, and cytotoxicity was determined using MTT assay. The IC_{50} value obtained for the EO was 1.25 μL/mL [39].

Sideritis montana L. subsp. montana is used as a diuretic and digestive aid. *S. montana* was collected in Camerino, Italy. The EO (yield of 0.07%) was analyzed using GC/MS, and the major compounds were germacrene D (20.8%), bicyclogermacrene (13.3%), and 8,13-abietadien-18-ol (10.2%). The cytotoxicity was tested

against MDA-MB-231 and HCT116 cell lines with IC_{50} values of 32.32 and 31.84 μg/mL, respectively [40].

Stachys annua L. is a perennial herb and small shrub. In the folk medicine of central Italy, its aerial parts have been used as anticatarrhal, antipyretic, tonic, and vulnerary (wound healing) agents. The EO isolated from its aerial parts was analyzed by GC/MS, and the major components were phytol (9.8%), germacrene D (9.2%), spathulenol (8.5%), and bicyclogermacrene (5.8%). The cytotoxic activity of the EO was determined by MTT assay. Analysis of the cytotoxicity against the HCT116, A375, and MDA-MB-231 cell lines showed IC_{50} values of 23.5, 37.2, and 41.5 μg/mL, respectively [41].

Plectranthus amboinicus Lour Spreng is cultivated in home gardens and is used in India for the treatment of cough, chronic asthma, and hiccough. The leaves of *P. amboinicus* were collected from a medicinal plant garden in Tamil, India. The cytotoxic activity of the EO was tested using MTT assay against the MCF-7 and HT-29 cell lines, and the IC_{50} values were 53 and 87 μg/mL, respectively [42].

Zhumeria majdae Rech. F. & Wendelbo is a medicinal plant endemic to Iran that is under the threat of extinction. This plant has been used as a curative agent for stomachache, flatulence, diarrhea, indigestion, cold, and headache, for wound healing and treatment of painful menstruation, and as an antiseptic. The aerial parts of *Z. majdae* were collected at five locations in Iran (S1, S2, S3, S4, and S5). The major components were trans-linalool oxide (18.7%), linalool (29.6%), and camphor (27.4%) at S1; trans-linalool oxide (28.6%), linalool (24.4%), and camphor (27.2%) at S2; trans-linalool oxide (16.2%), linalool (34.2%), and camphor (27.7%) at S3; trans-linalool oxide (14.6%), linalool (33.9%), and camphor (26.1%) at S4; and trans-linalool oxide (7.6%), linalool (34.6%), and camphor (34.7%) at S5. The cytotoxicity of the EOs was measured using MTT assay against A375 and MCF7 cell lines, with IC_{50} values of 746 (S1), 666 (S2), 624 (S3), 779 (S4), and 718 (S5) μg/mL and 674 (S1), 717 (S2), 732 (S3), 646 (S4), and 642 (S5), μg/mL, respectively [43].

Cedronella canariensis L. Webb & Berthel. (syn. *Dracocephalum canariense* L.) is present in the Canary Islands. It is a perennial herb, sometimes shrubby. The plant is used in traditional medicine as an anticatarrhal, tonic, antimicrobial, analgesic, carminative, diuretic, hypoglycemiant, hypotensive, and anti-inflammatory agent and decongestant of the respiratory tract. The EO was obtained from the aerial parts of *C. canariensis* collected in El Monte de las Mercedes, Canary Islands, Spain, in 2013 (yield of 2.5%). The EO was analyzed by GC/FID and GC/MS; pinocarvone (58.0%) and α-pinene (10.8%) were the main constituents. The cytotoxicity of the EO was evaluated against A345 (IC_{50} of 4.3 μg/mL), MDA-MB-231 (IC_{50} of 7.3 μg/mL), and HCT 116 (IC_{50} of 11.4 μg/mL) cell lines by MTT assay [44].

Rosmarinus officinalis L. EO is used as an antibacterial, cytotoxic, antimutagenic, antioxidant, antiphlogistic, and chemopreventive agent. The EO (yield of 0.23% w/w) was extracted from the plant collected in Guatemala. The IC_{50} values of the EO against AGS, A375, and A431 cell lines were 0.21, 0.24, and 0.41 μL/mL, respectively [22].

Teucrium yemense Delfi. possesses antifungal, antibacterial, larvicidal, antispasmodic, antioxidant, anti-inflammatory, antiulcer, hypoglycemic, antiacetylcholinesterase, and hepatoprotective activities. Its leaves were collected in two different provinces of Yemen: Dhamar (TY-d) and Taiz (TY-t). The EOs were analyzed, and the most abundant constituents of TY-d were (*E*)-caryophyllene (11.2%), α-humulene (4.0%), γ-selinene (5.5%), 7-epi-α-selinene (20.1%), and caryophyllene oxide (20.1%). The major compounds in TY-t were α-pinene (6.6%), (*E*)-caryophyllene (19.1%), α-humulene (6.4%), δ-cadinene (6.5%), caryophyllene oxide (4.3%), α-cadinol (9.5%), and shyobunol (4.6%). TY-d was active against the HT-29 cell line with an IC_{50} value of 43.7 μg/mL. TY-t was active against the MCF-7 and MDA-MB-231 cell lines (IC_{50} of 24.4 and 59.9 μg/mL, respectively) [45].

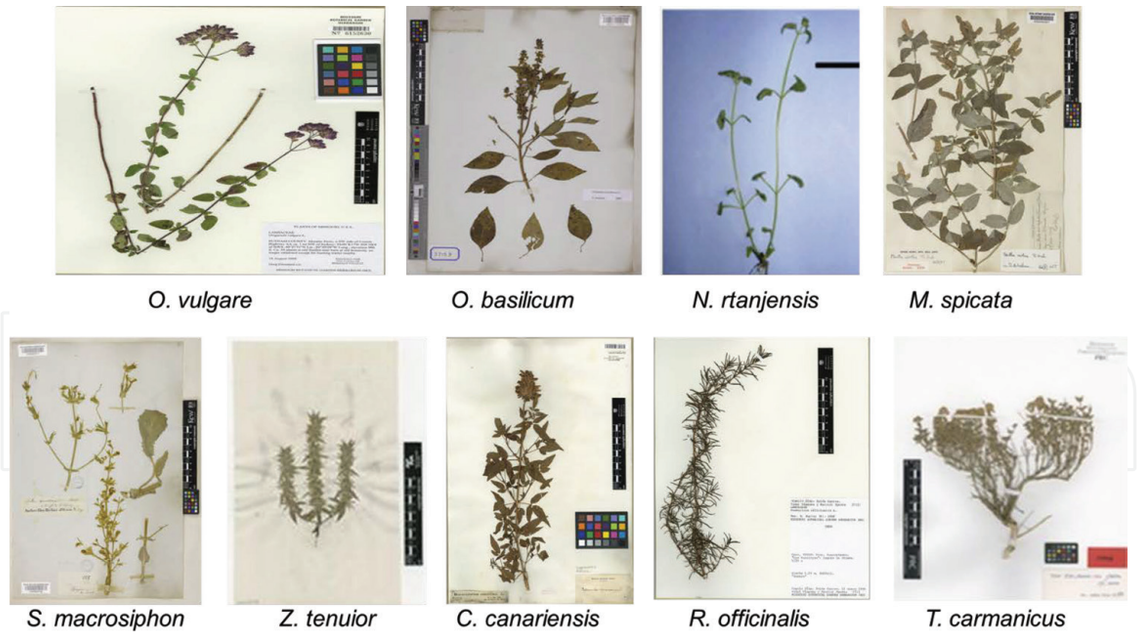

Figure 1.
Plants whose EOs present remarkable cytotoxic activity. Images taken from [48]. Image of N. rtanjensis taken from [49].

Premna microphylla Turcz. is broadly distributed in the eastern, middle, and southern regions of China. Leaves of *P. microphylla* are used to treat dysentery, appendicitis, and infections for their antioxidant and cytotoxic activities. The plant was collected in China. The EO was obtained with a yield of 0.31% w/w. The major components were blumenol C (49.7%), β-cedrene (6.1%), limonene (3.8%), α-guaiene (3.3%), cryptone (3.1%), and α-cyperone (2.7%). The EO was tested for its cytotoxic activity against HepG2 and MCF-7 cells, with IC_{50} values of 0.072 and 0.188 mg/mL, respectively [46].

Dracocephalum kotschyi Boiss is native to Iran. In traditional medicine, it is used to treat headaches, congestion, and liver disorders and for its antihyperlipidemic and anti-epimastigotic effects. The herb *D. kotschyi* is locally known as "Sama" in Lorestan Province. Aerial parts of wild *D. kotschyi* Boiss were collected in western Iran. A yellowish fragrant oil was obtained (yield of 0.16% w/w). The principal components of the EO were geranial (12.08%), α-pinene (10.34%), geraniol acetate (10.27%), geraniol (9.55%), neral (8.9%), limonene (6.95%), β-myrcene (3.42%), and β-pinene (2.18%). The IC_{50} against HeLa cell line was 26.4 μg/mL [47].

The National Cancer Institute of the USA (NCI) has screened approximately 100,000 compounds and 50,000 natural product extracts for potential anticancer agents [47]. The NCI considers a compound or an extract to have potential anticancer activity if it has an IC_{50} value of 4 or 30 μg/mL, respectively. Therefore, according to the NCI, the EOs described in this review with remarkable cytotoxic activity are those obtained from *O. basilicum, S. sahandica, O. vulgare, N. rtanjensis, M. spicata, S. macrosiphon, Z. tenuior, C. canariensis, R. officinalis*, and *T. carmanicus* (**Figure 1**).

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