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Top Edible Wild Plants of Eastern Mediterranean Region. Part I: Anticancer Activity

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Medicinal plants are the major source of natural products that are used for drug discovery and development. Cancer is second cause of disease-related deaths, after cardiovascular diseases. Numerous studies were conducted and published where plant materials such as extracts, essential oils, pure natural compounds or their combinations and formulations, were tested for the treatments of cancers, tumors, and their prevention. The fauna of the Middle East region, especially the area between the Mediterranean and the Jordan River (Israel and Palestine), includes some plant species with notable potential anticancer activity. Some of these plants, are known for this activity for centuries, as we know from the traditional medicines of this region. For example, *Arum palaestinum* is one of the most important plants used in folk medicine for the treatment of cancer, and modern studies have confirmed this property. Several natural products that were isolated from this plant were proposed as responsible for this activity. In this review we will introduce the most important edible plants (not including trees) and their published anticancer activity, as well as according to traditional medicine. Important natural product proposed for these activities will be presented, as well as selected mechanism of action. Based on this brief presentation, some future applications and research potentials will be suggested.

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1. INTRODUCTION

Plants were used by human since antiquity, mainly for nutritional purposes, but as early as the dawn of humanity, plants we used also for medicinal, therapeutical treatments [1,2,3]. Earliest known cancer cases were determined by archeologists to be around 1.8 million years ago [4]. Attempts to treat cancer, like other human health disorders, started also as early as human existence. The attitudes of the highly skilled ancient Egyptian physicians about cancer treatments were various. Some described cancer as “grave disease and there is no treatment for it”, while others used various methods to try to cure it [5]. One of the (untreated) cancer cases of antiquity that was thoroughly studied by modern science, was of a young adult from Northern Nubia, that belonged to ancient Egypt, dating about 1200 BC [6]. Ancient Greek physicians contributed their experience and knowledge for treatment of cancer, and some of this information is well documented [7].

Drug discovery from medicinal plants is one of the major sources for some final products, but mainly for prodrugs and starting materials [8]. In many cases, the developments of these modern drugs were based on traditional knowledge, such as the very well-known artemisinin and its modifications, that resulted a Noble prize in 2015 [9]. The drug discovery was based on the knowledge that *Artemisia annua*, the major source of artemisinin, is used in traditional Chinese medicine to treat Malaria.

Cancer is the second cause of disease-related deaths among humans, after cardiovascular complications [10], but it also affects animal, wild and domesticated [11]. The global annual costs of cancer related complications is around USD 193 billion, and it is estimated that this spending will be around USD 25.2 trillion over the next thirty years [12]. Cancer treatment and preventions drugs are numerous including natural and synthetic pure compounds, plant extracts, essential oils, mixtures, and formulations [13]. While synthetic drugs have medium to severe side effects [14], most known natural products and mixtures are notably unstable [13].

The search for anticancer therapies based on natural products is of a global concern since it has a potential of safe drugs development. These natural products can also ameliorate the side effects of synthetic drugs [15,16].

Eastern Mediterranean shores populations are known for their healthy nutritional habits, especially consuming healthy wild plants. The list of these plants is very long but the top ten edible wild plants, not including trees, alphabetically ordered, are: *Arum palaestinum* (Araceae), *Cichorium pumilum* (Syn. *Cichorium endivia*, Asteraceae), *Cyclamen persicum* (Primulaceae), *Foeniculum vulgare* (Apiaceae), *Gundelia tournefortii* (Asteraceae), *Majorana syriaca* (Syn. *Origanum syriacum*, Lamiaceae), *Malva Sylvestris* (Malvaceae), *Micromeria fruticosa* (Lamiaceae), *Salvia fruticosa* (Syn. *S. triloba*, *S. libanotica*, *S. cypria*, *S. lobryana*, Lamiaceae), *Sinapis alba* (Brassicaceae). From now on, these plants will be referred to in this review article as the “Deca-plants” (10 plants).

2. ETHNOBOTANY AND ETHNOMEDICINE OF THE DECA-PLANTS

The most important ethnobotanical use of the Deca-plants was and still is for human and livestock food, but we will focus in this review article on human nutrition. Different parts of the Deca-plants are eaten by humans in the discussed region, as shown in Table 1.

Besides for food, the Deca-plants were and still used in traditional medicine of this region, in the same manner they are used in other regions. Numerous ethnomedicinal uses are known and published. Among the most frequently mentioned: skin complications, urinary system disorders, gastric disorders, cancer and prostate disorders, arthritis, respiratory complications, diabetes, urinary system disorders, wound healing, teeth and gums problems, inflammations, bone disorders, antivenom, anti-plant toxicity, fertility disorders, general relaxation, and other ailments [17,18].

But in this article, we are focus on anticancer activities, so, the anticancer ethnomedicinal uses of the Deca-plants are presented in Table 2.

Table 1. Food uses of the deca-plants in eastern mediterranean region

Species	Consumed part/s	Major method/s of use
Arum palaestinum	Leaves (all other parts are toxic)	Fried in olive oil
Cichorium pumilum	Leaves and young stem	Cooked or fried with or without other food ingredients Herbal tea/infusion
	Flowers, fresh or dries Seeds	Herbal infusion, coffee substitute
Cyclamen persicum	Leaves (all other parts are toxic)	Stuffed with rice with or without meat
Foeniculum vulgare	Leaves and young stems	Eaten fresh, herbal tea/infusion, sweets flavoring
Gundelia tournefortii	Young stems, rarely young leaves, flowers after removing thorns	Cooked or fried with or without other food
Majorana syriaca	Leaves (mainly) and very young stems	Dried and added to many foods as a spice, eaten mixed with olive oil, fresh or dried are baked with bread
Malva sylvestris	Leaves (mainly) and very young stems	Cooked or fried with or without other food. Fresh used to prepare salads and rarely stuffed with rice
	Flowers Seeds, raw or dry	Eaten raw or in salads Eaten fresh or as salad dressing
Micromeria fruticosa	Leaves and stems	Herbal tea/infusion
Rumex pulcher	Leaves	Consumed raw in salads but mainly stuffed in pastries
Salvia fruticosa	Leaves (mainly), young stems and rarely flowers	Herbal tea/infusion, meat, poultry, fish dressing
Sinapis alba	Leaves and young stems	Fresh (mainly) or dried, consumed in salads
	Seeds	Used to prepare mustard or mustard oil, but also added to salads and cooked foods as a spice

Table 2. Anticancer ethnomedicinal uses of the Deca-plants in Eastern Mediterranean region

Species	Objectives and methods of use	Ref.
Arum palaestinum	Leaves, cooked or fried taken orally	[19,20]
	Leaves decoction taken orally	[21]
Cichorium pumilum	Aerial parts infusion taken orally	[19]
Cyclamen persicum	Leaves infusion taken orally	[19]
Foeniculum vulgare	Leaves and young stems, eaten fresh or infusion	[22]
Gundelia tournefortii	Aerial parts (excluding thorns) are cooked and eaten	[20]
Majorana syriaca	Leaves infusion taken orally	[19]
Malva sylvestris	Leaves infusion taken orally	[19]
Micromeria fruticosa	Leaves infusion taken orally	[19]
Salvia fruticosa	Leaves infusion taken orally	[19]
Sinapis alba	Leaves infusion taken orally [a]	[19]

Ref., references

a) This species is often confused by non-botanists with Sinapis arvensis.

3. ANTICANCER ACTIVITIES OF THE DECA-PLANTS AND THEIR NATURAL PRODUCTS

Modern research has noticed the traditional anticancer properties of the Deca-plants and they were extensively studied for this activity. The number of published reports about each plant are significantly different, where publications for some of them were a few, while for others the numbers of publications were notably large. In such cases, we chose the most significant. Anticancer activity of the Deca-plants is presented in Table 3.

Table 3. Published Anticancer Activities of the Deca-plants in Eastern Mediterranean region

Testing Method and Results	Ref.
Arum palaestinum	
New alkaloid (Fig. 1) was isolated from the ethyl acetate leaves extract. Both had cytotoxic effect on MCF-7 cells but not on HepG2 cells.	[23]
Leaves were extracted successively with water, ethyl acetate and *n*-butanol, affording new alkaloid (Fig. 1), which had cytotoxic activity against A549, SK-OV-3, SK-MEL-2 and HCT-15 cell lines.	[24]
Leaves ethanolic extract had significant activity against MCF-7 cell lines.	[25]
Aerial parts were extracted with 70% aqueous ethanol, and fractionated with diethyl ether, dichloromethane, ethyl acetate, *n*-butanol, methanol, and water. Paper chromatography yielded four polyphenolic (Fig. 2). Original extract and phenolics had clear activity against Hep2, HeLa, HepG2 and MCF7 cell lines.	[26]
Leaves and roots aqueous extract was formulated with isovanillin, linolenic acid and β-sitosterol, resulting in reduction of prostate tumors in mice.	[27]
Leaves were separately extracted with water and 1:1 methanol: dichloromethane (v/v). Both extracts were active against C2Cl2, 3T3-L1, HeLa cell lines.	[28]
Leaves were separately extracted with ethyl acetate, methanol, chloroform, and water. Extracts had activity against HCT116, PC3, MCF-7 cell lines, where ethyl acetate extract showed the highest activity.	[29]
Aerial parts were extracted and successively fractionized with a series of solvents with increasing polarity. Extracts and fractions were analyzed, and some know phenolics were isolated, with two chrysoeriol glucosides isolated from this plant for the first time. Some extracts and compounds had activity against MCF7, HepG2, Hep2 and HeLa cell lines.	[30]
Leaves and roots aqueous extract in combination with (ready) extracts of *Peganum harmala* and *Curcuma longa*; as well as combinations of natural (curcumin, harmine and isovanillin) and synthetic anticancer compounds. The combinations showed activity according to various *in vitro* and *in vivo* anticancer biomarkers.	[31]
Aqueous flowers extract was found active against Hep3B cell lines.	[32]
Cichorium pumilum	
Aerial parts were extracted with microwave-assisted 50% aqueous ethanol. The extract has positive effect on dimethylbenz[a]anthracene-induced cancer in female rats, tested with histological and biochemical biomarkers.	[33]
Roots methanolic extract was active against HCT-116 human cancer cells. Extract was analyzed for phenolics, resulting in catechin as major component.	[34]
Shoots and roots methanolic extract was active against MFC-7 cell lines. Extract was analyzed for phenolics, with results almost identical to the previous report.	[35]
Leaves aqueous extract was active against 1.2-dimethyl hydrazine-induced cancer in mice. The highest dose of 600 mg/kg body weight was most efficient.	[36]
Cyclamen persicum	
Dried tubers were extracted with 70% aqueous methanol, yielding saxifragifolin B and cyclamin (Fig. 3). Both compounds were tested against SK-BR-3, HT-29, HepG2/3A, NCI-H1299, BXPC-3, 22RV1 cell lines. Saxifragifolin B was more active.	[37]
Tubers and leaves were separately extracted with 70% aqueous ethanol, and extracts were tested in various concentrations against MCF-7, PC-3 and LNCaP cancer cell lines. Both extracts had strong effect on MCF-7, PC-3 cells and less effect on LNCaP. Tubers	[38]

Testing Method and Results	Ref.
extracts had a way stronger effect.	
Tubers of three species of *Cyclamen* were extracted with 95% aqueous ethanol and the extracts were tested against H1975 and HCC78 cancer cell lines. *C. persicum* had the strongest effect, with cell viability of 0% cell viability for H1975 cells in concentrations greater than 75 µg/mL, and around 7% for HCC78 cells in concentrations greater than 150 µg/mL.	[39]
Leaves and flowers of three *Cyclamen* species were separately extracted with water. Extracts were tested against MDA-MB-231 cell lines. *C. persecum* leaves extract was most potent, and this species exceeded the other two in other activities: total phenolic content, total flavonoid content, and antioxidant activity.	[40]
Foeniculum vulgare	
Seeds were extracted with 70% aqueous methanol, and extract was active against B16F10 melanoma cell line.	[41]
Seeds essential oil (EO) and 50% aqueous methanolic extract were prepared. Both products were tested and found active in both *in vitro* (against MCF-7, HepG2, HT-29, HeLa, H460 and U251 cell lines), and *in vivo* (irradiation-induced cancer in mice). Chemical composition of was determined by GC-MS and the three major constituents (all previously known) are shown in Fig. 4.	[42]
Aerial parts (excluding flowers) were extracted with 50% methanol, and the extract had apoptosis activity against HeLa cells.	[43]
Fruits were extracted with 96% aqueous ethanol, and extract had notable activity against MCF-7 cancer cells (IC_{50} = 69.41 ppm). In this study, two other plant extracts were studied: *Trigonella foenum-graecum* and *Aglaia elliptica*. Their IC_{50} values are, 241.24 and 19.44 ppm, respectively.	[44]
Fresh leaves essential oil (EO) was tested against 9 different cancer cell lines, along with EO's of three other plants, and it had small effect. The chemical composition of the EO was analyzed by GC-MS resulting *E*-anethole, myrcene, α-pinene, fenchone (Fig. 5), and, L-limonene, estragol, (Fig. 4).	[45]
Aerial parts essential oil (EO) was tested against 6 different cancer cells, showing moderate effect. The chemical composition of the EO was analyzed by GC-MS.	[46]
This research is similar to above cited studies [42,45,46] but with better results (IC_{50} = 10 ppm).	[47]
Aerial parts essential oils of *F. volgare* and *Pelargonium graveolens* were prepared, and their activity against MCF-7 cancer cells was tested, separately and as a mixture. In both cases the effect was moderate. The composition of both EO's was analyzed with GC-MS.	[48]
Very similar study to [42,45-47] with one difference: seeds were harvested in different locations and several EO's were prepared and tested.	[49]
Aqueous seeds extract was analyzed to isolate proteins that were active against MCF-7 cancer cells (inhibition of 65-80% at 100 ppm).	[50]
Mice were infected with 4T1 cancer cells, then treated with seeds aqueous extract, which resulted clear activity compared with control untreated groups.	[51]
Very similar study to [42, 45-47, 49] with two differences: the EO was commercially purchased, and it was tested against different cancer cell lines. The result was weak to moderate activity. In this study, the EO's of 15 more plants were investigated and they were analyzed for chemical compositions.	[52]
Seeds were extracted with 75% aqueous ethanol, and extract was found highly active against NCI-H446 and NCI-H661 cancer cell lines. A mechanism of action is proposed as partial down regulation of Bcl-2 (B-cell lymphoma 2 protein).	[53]
Same research group of previous work [53] used the same methods but different cancer cell lines (QGY-7701, Bel-7404 and HHL-5). Studying the mechanism of action revealed that extract inhibited Survivin protein in these cells.	[54]
Same research group, same methods and same results like in [51]. Seeds methanolic extract had significant activity against A549 human lung cancer cells. Computer simulation (molecular docking, *in silico*) of major secondary metabolites of the	[55]

Testing Method and Results	Ref.
plant, limonene and α-pinene, that proved that they have potential of anticancer agents.	[56]
EO of the fruits of ssp. *Piperitum* was prepared and testes against MDA-MB231cancer cells. It showed notable prevention and inhibition activities.	[57]
A follow up of studies [51,55] with investigation of mechanism biomarkers: treatment down regulated HSP70 and HSP90 (heat shock protein).	
95% Aqueous ethanol, ultrasound-assisted extractions of seeds yielded and extract that was tested against MCF-7 and MDA-MB435 cancer cell lines. For the first it had weak activity compared with seven other plans, and for the second, it had relatively strong activity. The extract was analyzed with GC-MS resulting notably different composition (Fig. 6) compared with previous reports (Fig. 4, [42], and Fig. 5, [45]).	[58] [59] [60]
Gundelia tournefortii	
The edible parts, stems and flowers (excluding prickles) were separately extracted with water, methanol, and *n*-hexane. Extracts were tested against HCT-116 cancer cells resulting IC_{50} > 1000 µg/mL (inactive). Extracts were analyzed for chemical compositions by GC-MS, and the major compounds are listed, and their structures are presented in the article.	[61]
Roots and leaves were separately extracted with water, and both extracts were active against MCF-7 cell lines, resulting moderate activity. Essential oil was also prepared but was not tested for anticancer activity.	[62]
Seeds aqueous extract was found moderately active against six cancer cell lines. Extract was analyzed by GC-MS and major constituents are shown in Fig 7.	[63]
Aerial parts aqueous extract was tested against Hep3B cancer cells injected in mice and found active. Decrease of p53/Akt/PI3K signaling pathway was proposed as mechanism of action.	[64]
A follow up of the previous study, with the same methods and very similar results.	[65]
Majorana syriaca	
Aerial parts ethanolic extract had significant activity against MCF-7 cell lines.	[25]
Essential oil (EO), aqueous and 70% aqueous ethanol extracts, were separately prepared from dry leaves. Both materials were tested against MCF-7 cancer cells. For concentration of 50 µg/mL and 72 h, cell survival was: 25.1% for ethanolic extract, 25.2% for aqueous extract and 21.3% for EO. EO was analyzed with GC-MS and major compounds are presented in Fig. 8.	[66]
Aerial parts were extracted with 40% aqueous ethanol and was active against THP-1 human leukemia cells.	[67]
EO and 80% aqueous ethanol extract were separately prepared, and both were active against two cancer cell lines. Authors indicate that the plants they used were cultivated in Cairo university, not wild.	[68]
70% Aqueous ethanolic extract was moderately active against LoVo and SW620 cancer cells.	[69]
Fresh leaves aqueous extract had activity against MDA-MB231 cancer cells.	[70]
A follow up of the previous study with 80% aqueous ethanol dry leaves extract.	[71]
Malva sylvestris	
Leaves were extracted with 70% aqueous methanol and extract was treated for isolation of phenolics (pH=2). Extract was tested against B16, A375 and CHP100 cell lines, and found active, mainly against A375 (human melanoma) cells. HPLC analysis of the extract yielded compounds shown in Fig. 9.	[72]
Essential oils (EO's) of aerial parts of plants from 16 different locations were prepared and found active against C32, MCF-7 and SkBr3 cell lines. EO's were also analyzed for chemical compositions.	[73]
Leaves ethanolic extract was moderately active against HeLa cell line.	[74]
Leaves were extracted with 80% aqueous ethanol, and extract was found active against two types of cell lines (not specified). It was also analyzed by GC-MS.	[75]
80% Ethanolic aqueous extract of leaves had high activity against MCF-7 and Hep2 cell	[76]

Testing Method and Results	Ref.
lines.	
Micromeria fruticosa	
Aerial parts aqueous extract and essential oil were prepared and tested against MCF-7 and HCT cancer cells, showing very strong activity. In concentration of 50 µg/mL, survival of MCF-7 cells was 25% for extract and 10% for EO, while for HCT cells, results were 21% and 14%, respectively, the chemical composition of EO was analyzed with GC-MS, and major constituents are shown in Fig. 10.	[77]
Aerial parts aqueous extract had moderate activity against U-87 MG cancer cells: at concentration of 200 µg/mL, cells survival was 30%.	[78]
Aerial parts were extracted with methanol and extract was tested against MCF-7 and HCT-116 cancer cells. Testing was performed for several biomarkers of cell viability and apoptosis, including caspase activity. In all tests, extract showed high potency.	[79]
Aerial parts were extracted with methanol and extract was tested against MCF-7 and HCT-116 cancer cells. This study is a follow up of studies [77,79], and its objective was to find the mechanism of action: downregulation of CDK1 and cyclin B1.	[80]
Ethanolic extract of aerial parts showed notable activity against MCF-7 and A549 cell lines. When combined with *Teucrium polium* ethanolic extract or cisplatin, synergetic effect was clear.	[81]
Leaves, stems, flowers, and roots were separately extracted with three solvents: water, ethanol, and *n*-hexane (12 extracts). Each was tested against human colon cancer cells, showing different levels of activity, in different concentrations and duration. Extracts were analyzed with GC-MS resulting very similar compositions as in study [77], with additional compound: oleamide, *cis*-$CH_3(CH_2)_7CH{=}CH(CH_2)_7CONH_2$	[82]
Salvia fruticosa	
Essential oil (EO), aqueous and 70% aqueous ethanol extracts, were separately prepared from dry leaves. Both materials were tested against MCF-7 cancer cells. For concentration of 50 µg/mL and 72 h, cell survival was: 14.9% for ethanolic extract, 27.9% for aqueous extract and 13.3% for EO. EO was analyzed with GC-MS and major compounds are presented in Fig. 11.	[66]
Combinations of compounds shown in Fig. 11 had clear activity against HCT-116 cancer cells. Mechanism of action was studied revealing caspase inhibition.	[83]
Aerial parts aqueous extract was tested against HCT15 and CO115 cancer cells, showing notable activity. This activity was separately compared with same extract of *Salvia officinalis* and rosmarinic (an important constituent of aqueous sage extracts) and was higher that both.	[84]
Aqueous extract was prepared and was also analyzed to isolate rosmarinic acid and luteolin-7-glucoside (Fig. 12). All three materials had activity against Caco-2 and HeLa cell lines, as well as DNA damage repair.	[85]
Methanolic extract of commercial, dry aerial parts powder was prepared and analyzed with GC-MS, resulting some known compounds showed in previous figures. This extract was active against PC-3 and DU-145 cell lines and had DNA damage repairing activity.	[86]
Aerial parts methanolic extract was prepared, separately fractionized with methanol and *n*-hexane. The three materials were analyzed with GC-MS, resulting some compounds shown in previous figures as well as salvigenin and viridiflorol (Fig. 13). Extract and fractions were active against MCF-7, MDA-MB-231, RKO, Caco-2 and 3T3-L1 cell lines. Bark methanolic extract was active against MCF-7, T47D and MDA-MB-468 cell lines, with inhibition of 65, 72 and 76%, respectively.	[87]
Aerial parts were extracted consecutively with petroleum ether, dichloromethane, methanol, and water. All extracts were tested against A375., A431 and HaCaT cell lines, but only methanolic extract had significant activity.	[88]
Roots were extracted with acetone, and column chromatography of extract yielded eight abietane diterpenoids (Fig. 14). Extract and isolated compounds were tested against HCT-116 and MDA-MB-132 cell lines. Compound 5 was most active with IC_{50} = 18 µM against HCT-116 cells, and 44 µM against MDA-MB-132 cells. Extract had IC_{50} values of	[89]

Testing Method and Results	Ref.
177 and 110 µM, respectively.	[90]
Leaves were separately extracted with 90% aqueous ethanol and acetone. Both extracts were tested against U2OS and SKOV3 cancer cells: acetone extract had higher activity.	[91]
Sinapis alba	
Mucilage fraction was isolated from seeds (slightly basic aqueous solution, 65 ◦C), and it was fed to mice and rats with cancer that was induced by azoxymethane. Cancer was reduced in both cases.	[92]
Seeds were extracted with ethanol and diethyl ether. Extract was active *in vitro* (against SW480 and NIH/3T3 cancer cells) and *in vivo* (mice with cancer that was induced by azoxymethane).	[93]
Seeds and leaves were extracted with 80% aqueous ethanol. Extract was analyzed and two natural products were isolated: sinalbin and sinigrin. The three materials were tested against HCT-116 cancer cells: sinigrin had no activity, and sinablin had weak activity compared with the extract, which was notably active.	[94]
Seeds powder was exposed to aqueous myrosinase that hydrolyzed sinigrin yielding allyl isothiocayante-rich powder (see Discussion). This was administered to rat with colon cancer (71.5 mg/kg), resulting clear cancer reduction.	[95]

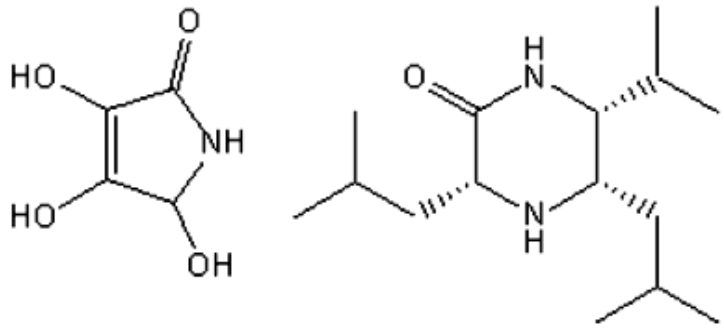

Fig. 1. New alkaloids with anticancer activity isolated from *Arum palaestinum* [23,24]

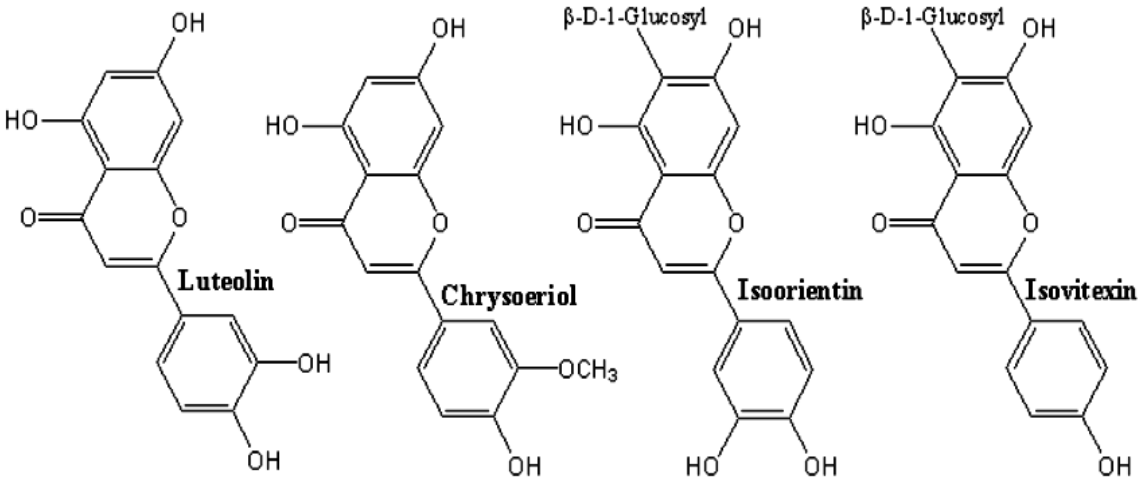

Fig. 2. Polyphenols with anticancer activity isolated from *Arum palaestimum* [26]

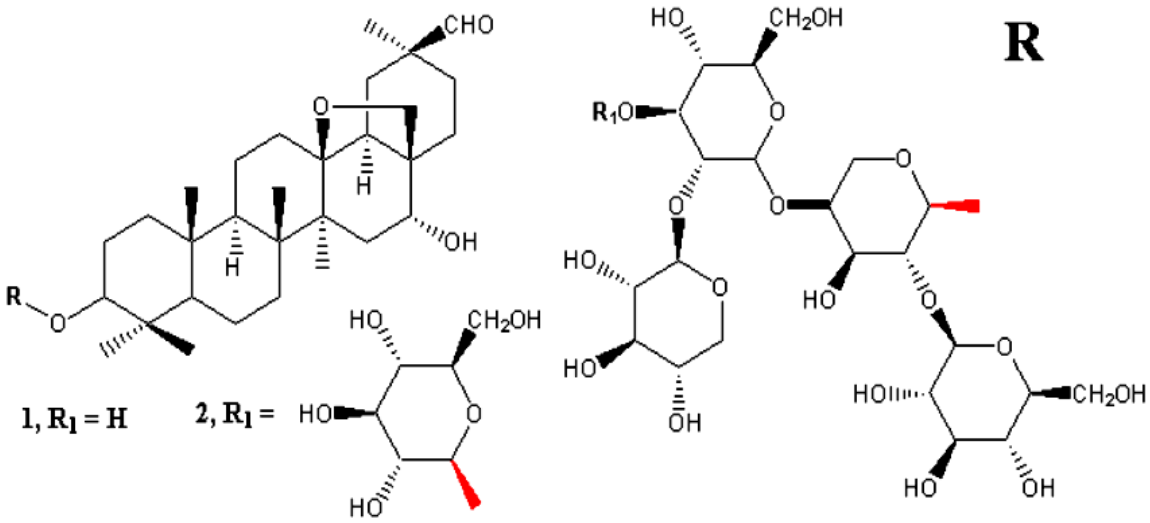

Fig. 3. Saxifragifolin B (1) and cyclamen (2) isolated from *Cyclamen persicum* [37]

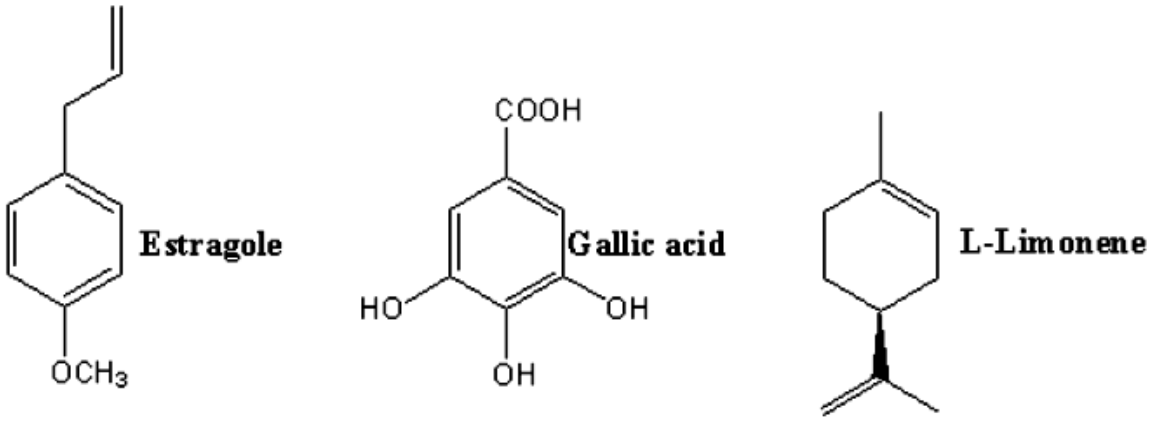

Fig. 4. Three major constituents of seeds essential oil of *Foeniculum vulgare* [42]

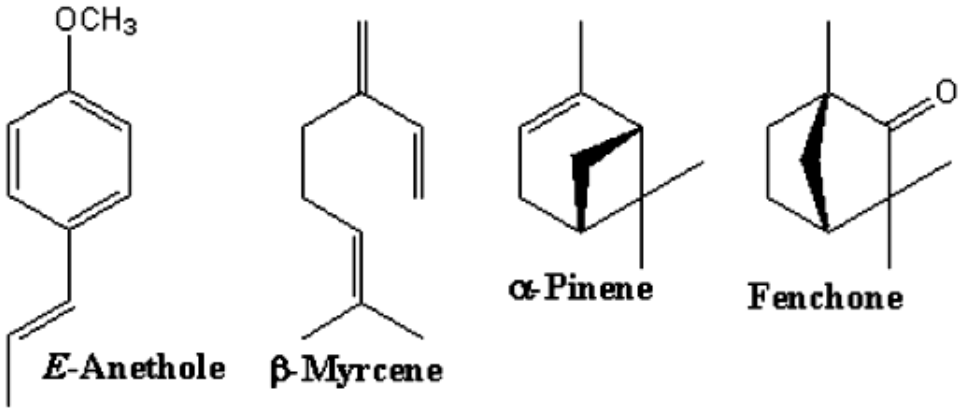

Fig. 5. Some major constituents of fresh leaves essential oil of *Foeniculum vulgare* [45]

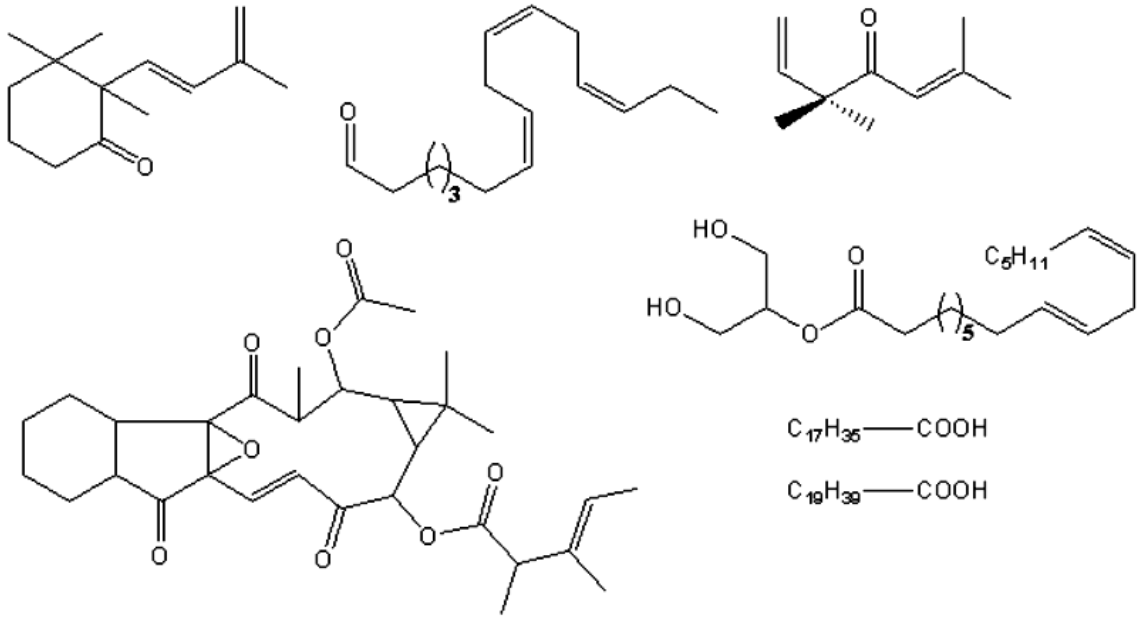

Fig. 6. Some major constituents of seeds extract of *Foeniculum vulgare* [60]

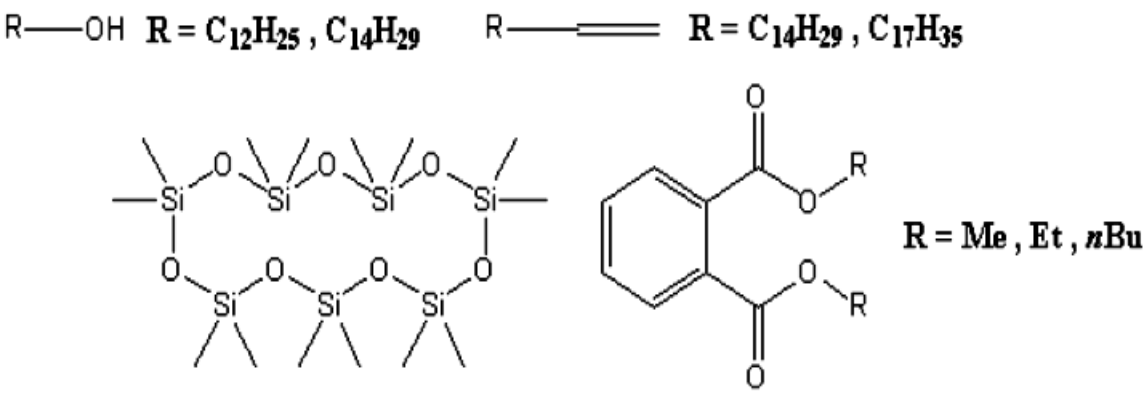

Fig. 7. Some major constituents of seeds extract of *Gundelia tournefortii* [63]

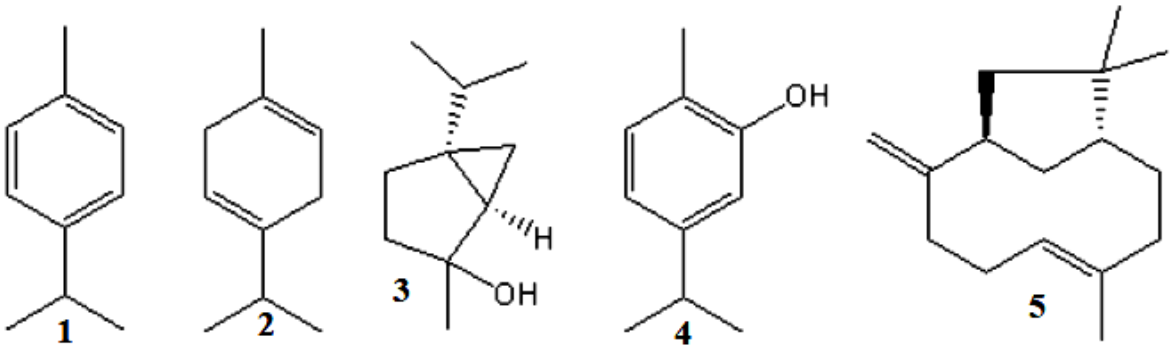

Fig. 8. Some major constituents of leaves essential oil of *Majorana syriaca* [66]

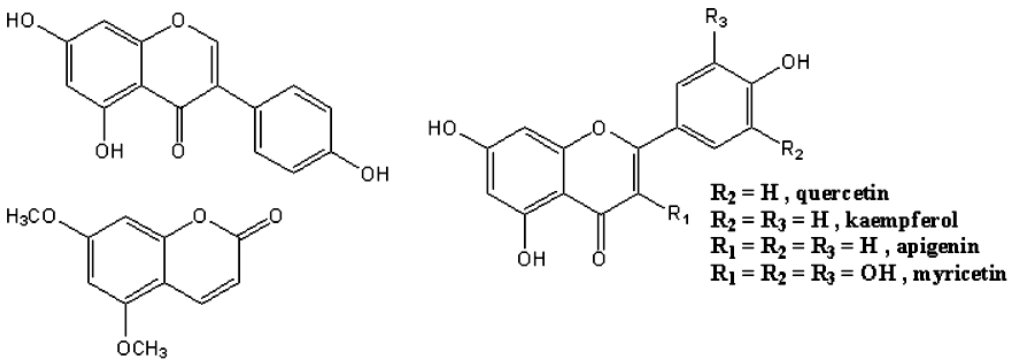

Fig. 9. Some major phenolics of methanolic leaves extract of *Malva sylvestris* [72]

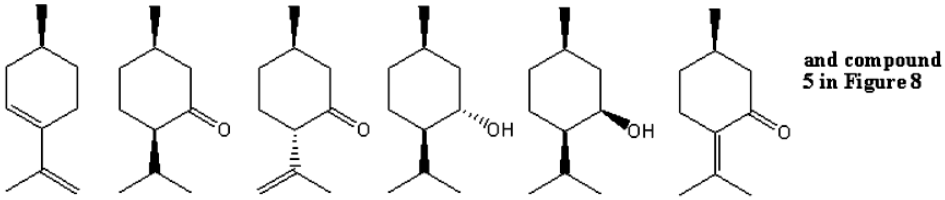

Fig. 10. Some major constituents of aerial parts essential oil of *Micromeria fruticosa* [77]

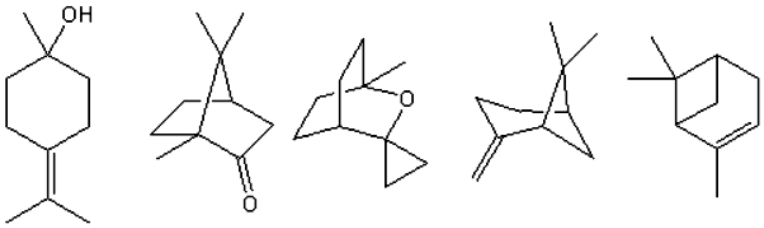

Fig. 11. Some major constituents of leaves essential oil of *Salvia fruticosa* [66]

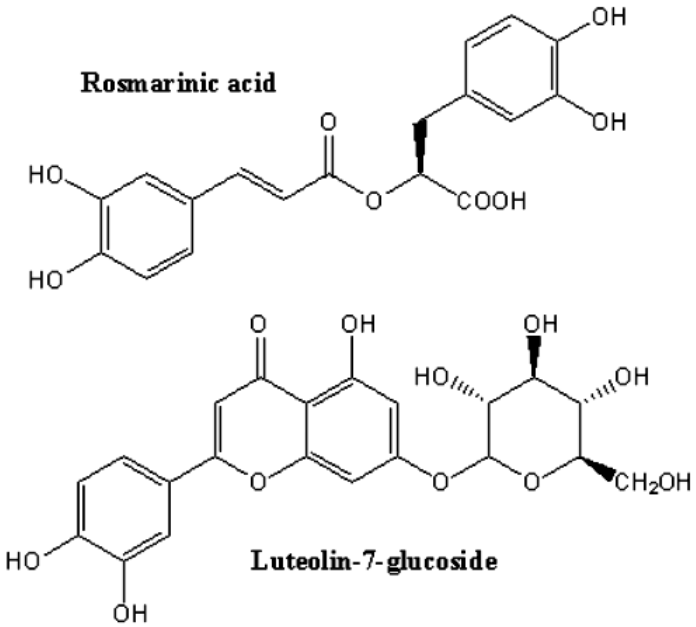

Fig. 12. Phenolics from aerial parts aqueous extract of *Salvia fruticosa* [85]

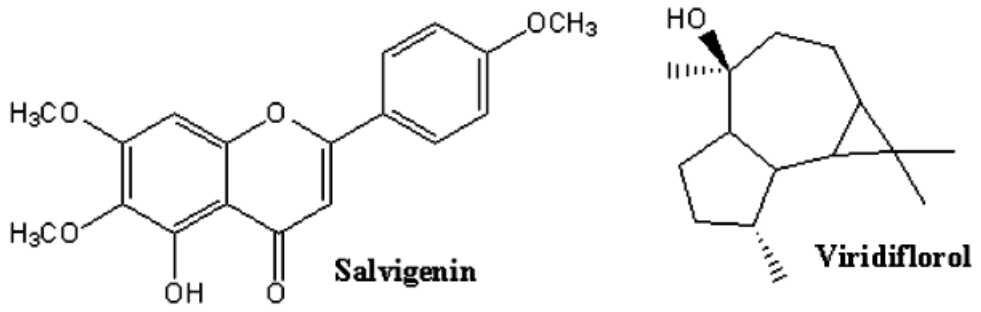

Fig. 13. Constituents from aerial parts methanolic extract of *Salvia fruticosa* [87]

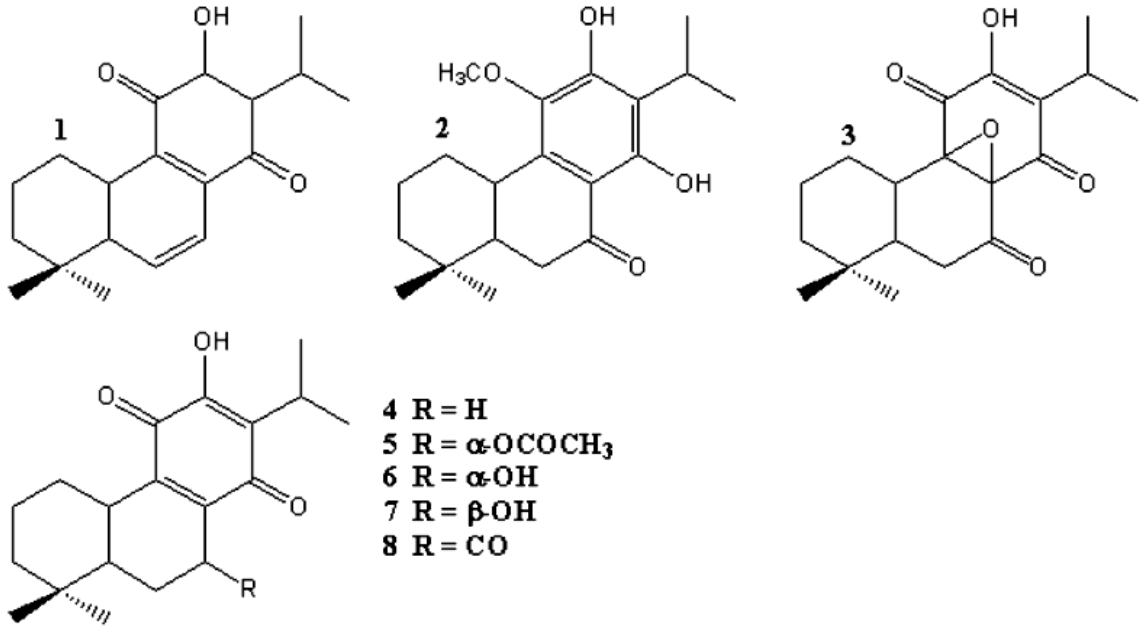

Fig. 14. abietane diterpenoids from roots acetone extract of *Salvia fruticosa* [90]

4. DISCUSSION

The search for cancer therapies is one of the most expanded fields of science, and it emerges from the critical need of humanity to combat this fatal illness. Synthetic drugs of almost all kinds and structures of compounds, but small molecules are the leading agents so far [96]. But the vast majority of synthetic drugs have adverse side effects [97], and cisplatin is the most known case in particular [98]. On this basis, the search for natural or seminatural therapies is more than obvious, and extracts, pure natural products or their analogues are investigated for this purpose [99,100].

Arum palaestinum is consumed during winter and early spring in the reviewed region of Eastern Mediterranean, and in folk medicines, it is considered an active anticancer plant. The chemical basis of this traditional practice was shown in many modern studies. This plant contains active alkaloids (Fig. 1, [23,24]), and it is known that this natural products family has the anticancer potency [101]. To give this statement further verification, study [31] reported that *A. palaestinum* extract was used in combination with extracts of *Peganum harmala* and *Curcuma longa*; as well as combinations of natural (curcumin, harmine and isovanillin) and synthetic anticancer compounds. *P. harmala*, a well-known alkaloid containing plant, is also known for its anticancer activity [102]. And even though *C. longa* is not an alkaloid-rich plant, but it is known for its anticancer properties [103]. The anticancer activity was also reported for the major active natural products of these plants: harmine (*P. harmala*, [104]) and curcumin (*C. longa*, [105]).

The anticancer activity of combinations of *A. palaestinum* with pure natural products isovanillin, linolenic acid and β-sitosterol; [27]), can indicate synergistic effects. The plant itself contains active anticancer polyphenols (Fig. 2, [26]), and this is consistent with the previously known effect of these compounds [106]. And continuing the topic of combinations, it is important to mention that despite the notable proximity of the structures of vanillin and its isomer, isovanillin (Fig. 15), the first was reported for its anticancer activity as a pure compound [107], while the second is anticancer agent only in combinations [27].

To conclude the discussion of *A. palaestinum* it is important to mention two published studies. First, the comprehensive metabolites analysis that was published by I.M. Abu-Reidah and his colleagues [108], where they reported the presence of 191 compounds. Second, A. Maree and his colleagues reported that they reviewed all documented cases of *A. palaestinum* poisoning in Israel and found no severe cases or deaths [109]. The edible part of this plant is the leaves and eating them fresh causes serious mouth irritation (oxalates). But no documented reports are known about consumption of other parts.

Many botanical authorities consider *Cichorium pumilum* and *Cichorium endivia* as the same species [110,111,112], while others consider *C. pumilum* only a subspecies of *C. endivia* [113]. However, in this article they are considered the same species. But it should clearly said, that even though few literature resources consider *C. pumilum* and *C. intybus* the same species (or ssp.), we will not present the anticancer activity of *C. intybus* despite the fact that it is interesting [114].

Published studies did report so far, the active compound/s in *C. pumilum* which is responsible for the plant anticancer property. But it can be reasonably assumed that this activity can be easily linked with β-ionone and/or its derivatives. Leaves of the plant (edible part) were extracted with nonpolar solvent (1:2 *n*-pentane-dichloromethane) and the extract was column chromatography, revealing the presence of β-ionone and its 5,6-epoxy (Fig. 16, compounds 1,2, [115]). In later study, aerial parts were extracted with ethanol and analyzed with the same method, yielding three norisoprenoids that have close structures to β-ionone (Fig. 16, structures 3,4, [116]). Several studies have shown that β-ionone and some of its natural and synthetic analogues have anticancer activities [117].

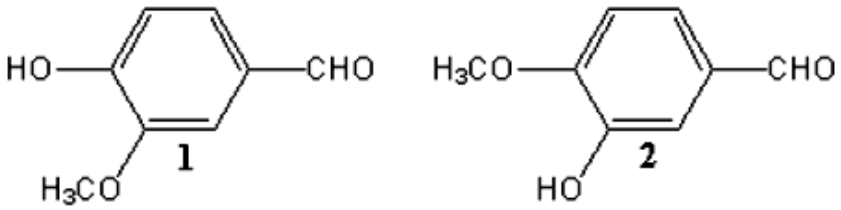

Fig. 15. Vanillin (1) and isovanillin (2)

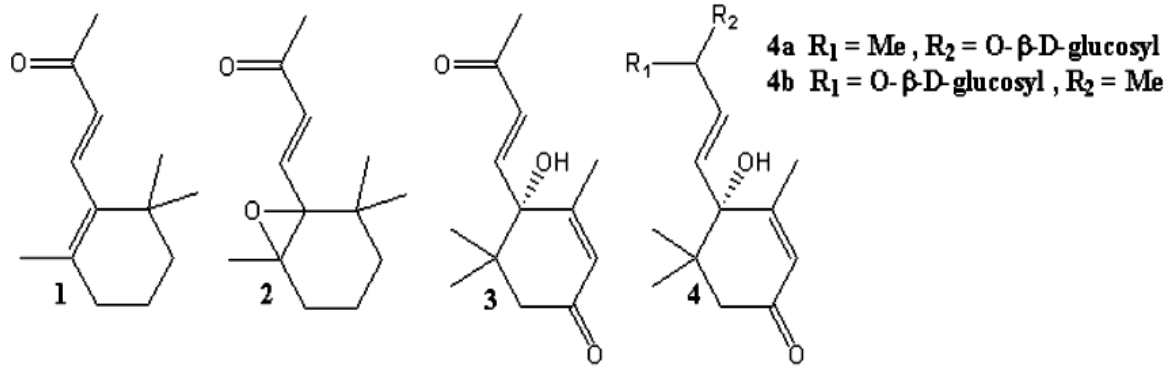

Fig. 16. Compounds with anticancer potency isolated from *Cichorium pumilum* [115,116]

Safety issues related to use of medicinal plants were always of a major concern, regardless with the nature of the use of these plants, but this concern is more intense when these plants are used for human nutrition [118]. Among the plants reviewed in this article for anticancer activity, a special attention was given to *Arum palaestinum*, *Foeniculum vulgare*, *Majorana syriaca*, *Malva Sylvestris* and *Salvia fruticosa* [119]. Interestingly, no safety concerns were mentioned regarding *Cyclamen persicum*. Authors of the previous article are local scholars that use wild *C. persicum* as food, and hence use the leaves, while authors from Europe, mostly use domesticated and cultivated varieties of this plant in gardens. So, Middle Eastern scholars raised no safety issues, but their European counterparts focused on the poisonous properties of the plant tubers, especially to pets and livestock [120,121]. Leaves of *C. persicum* are not only non-toxic, but they are also very nutritious: high phenolics and flavonoids content, strong antioxidant, with neoxanthin, violaxanthin, lutein, β−carotene, cis−β−carotene [40].

Seeds essential oil of *Foeniculum vulgare* was reported as active anticancer, and its major component is estragole (Fig. 4, [42]). This compound was found to have the same property as pure compound: against HepG2 [122], and against MCF-7 [123], cancer cells. The reported activity of the extract against HepG2 was IC_{50} 48 µg/mL, and the activity of the pure compound was 22 µg/mL. An opposing trend was found for MCF-7: extract 50 µg/mL and pure estragole 75 µg/mL. These results need more studies and explanations.

The search for anticancer natural products and their analogues and modifications, led scientists to explore nanoparticles that were prepared using plant materials [124]. Among these, silver nanoparticles (Ag-NPs) are very common, and one of them, with anticancer activity, was prepared using aqueous extract of *Malva sylvestris* as a reductant of silver ions [125]. These Ag-NPs had IC_{50} (72 h, µg/mL) of 36 against SK-OV-3 and 49 against OVCAR-3 cancer cells.

M. sylvestris as well as other *Malva* species, are known for high phenolics content, and thus, high antioxidant capacity [126]. Six of these phenolics are shown in Fig. 9 [72]. But one of the most important polyphenols of *M. sylvestris*, which can be found in high concentrations in the leaves (most consumed part) and has notable anticancer activity; was not mentioned so far: malvidin (Fig. 17, [127]).

A. Bhattacharya and his colleagues used exposed seeds powder to aqueous myrosinase that hydrolyzed sinigrin resulting allyl isothiocayante-rich powder, which consequently had anticancer activity [95]. This process (Fig. 18) was extensively studied by A. Tarar and his colleagues [128], with clear mechanism-studying orientation.

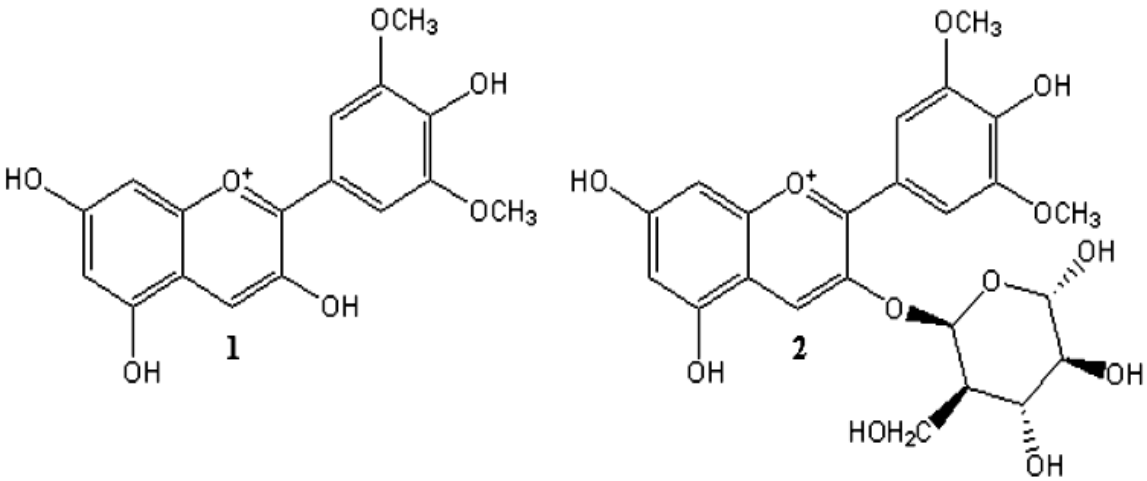

Fig. 17. Malvidin (aglycone, 1) and its glucoside (2) isolated from *Malva sylvestris* [127]

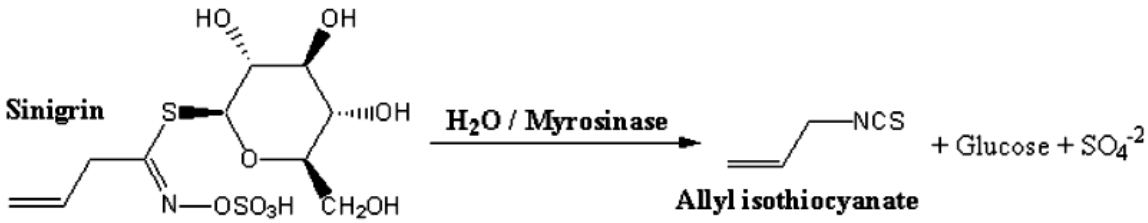

Fig. 18. Hydrolysis of sinigrin (*Siapis alba*) by myrosinase [128]

5. CONCLUSIONS

1) Top ten edible plants (Deca-plants) in Eastern Mediterranean region are very healthy foods, due to their nutritional and medicinal properties.
2) Anticancer activities of these plants were reasonably studied, but research should be expanded to understand the mechanism of action the underlies behind each activity.
3) As far as the edible parts of these plants in the reviewed region, there are no safety issues related to the consumption of these plants.
4) Anticancer activities of these plants should be more studied for nonedible parts.
5) Synergistic effects of these plants as combinations of their products, as well as with other plants, pure natural products, and synthetic anticancer drugs; should be more extensively studied.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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