Top Edible Wild Plants of Eastern Mediterranean Region. Part II: Anti-inflammatory Activity

Abstract:

In the first part of this series of review articles, we presented the anticancer activities of the most important wild edible plants of eastern Mediterranean region, which we named as the "Deca-plants" (D-P). In this review article, we will present the anti-inflammatory activities of these very important plants. After a brief introduction, anti-inflammatory activities of the D-P will be introduced in both traditional medicine of the peoples of this region, and in published scientific literature. Methods of use will be presented in the first part, and methods of testing and results, for modern research. In both cases, some of the D-Phave notable anti-inflammatory activities. In the extensive discussion section of this article, a major focus will be presented for anti-inflammatory activities of natural products contained in these plants, and some comparisons will be made with other plants. At this point, it is worth mentioning that the D-P have notably different number of anti-inflammatory activity reports, where on the top of them *Foeniculum vulgare* can be found. Contrary to that and to the best of our knowledge, *Cyclamen persicum* was not published for anti-inflammatory activity, even though some of its secondary metabolites are very well known for having this activity.Finally, the conclusions of this article will be accompanied with recommendations for future research.

Keywords: anti-inflammatory, medicinal plants, traditional medicine, plant extracts, essential oils, natural products, norisoprenoids, isothiocyanates

1. Introduction

Inflammation is a natural response of the immune system to damage triggered by various factors such as pathogens, cell damage and toxic materials [1]. This response, inflammation, can occur with many mechanisms in all body parts, especially major organs: heart, liver, pancreas, lungs, kidney, intestinal track, reproductive system and the brain.

Inflammation involved in the vast majority of sicknesses [2,3], and the treatments of these health disorders start with the treatment of inflammations that resulted them. **Figure 1** summarizes the inflammation-disease relationships for major chronic diseases.

Figure 1. Inflammation and major chronic diseases

Until today (August 2023), 22 synthetic, nonsteroidal anti-inflammatory drugs (NSAID's) where approved by the USA Food and Drug Agency (FDA) [4]. Even though most of them have relatively high efficiency, their side and adverse effects of most of them are also well known, and some are relatively severe [5].

Since ancient times, humans tried to use their food not only as nutritional source, but also to treat health disorder, and in this sense, medicinal plants have very important role. This approach is increasingly adopted by modern medicine for treatment of almost all health ailments, and inflammation is among the top of these [6]. So, since the Mediterranean diet is one of the healthiest on Earth [7], recent modern studies are approving the capacity of this diet in combating chronic diseases and inflammation [8].

2. Ethnomedicinal Anti-inflammatory Activities of the D-P

In the first part of this article series which presented the anticancer activity of the D-P, we extensively presented their ethnobotanical uses, especially as nutritional source [9]. So, in this article only the ethnomedicinal anti-inflammatory activity.

Interestingly, the D-P were rarelyreported to have notable anti-inflammatory activity in the ethnomedicine of the reviewed region. O. Said and his colleagues reported traditional medicine us of *Cyclamen persicum* to treat skin inflammations;*Majorana syriaca*,*Micromeriafruticosa* and*Salvia fruticosa* against intestinal inflammation [10].

In a follow-up review article, H. Azaizeh and his colleagues reported ethnomedicinal treatment of bacterial infections with *Cichorium pumilum* and*Salvia fruticosa*for intestinal inflammation [11]. In the same year of 2006, E. Lev reported in a review article that *Foeniculum vulgare* and *Salvia fruticosa*are used to treat intestinal diseases, but he did

notclearly indicate inflammations [12].He also mentioned *Sinapis alba* for treatment of infections.

Even though*Gundeliatournefortii*was not mentioned by the previous groups for ethnomedicinal use as anti-inflammatory treatment, M. Asadi-Samani and his colleagues indicated that this plant is used for this purpose, without specifying the type of inflammation or the treatment method [13].Finally, S. Oran and D. Al-Eisawi reported the use of *Cichorium pumilum* to treat eczema [14].

3. Anti-inflammatory Activities of the Deca-plants and Their Natural Products

The results of modern research of the anti-inflammatory activities of the D-P were published in a few dozens of articles. As we mentioned earlier, the number of these published studies notably differ from one plant to another. But these differences relate also to the natural products responsible for these activities, where in some of the D-P they were isolated and characterized and in others they were not.Anti-inflammatory activity of the D-P is presented in **Table 1**.

Table 1. Published Anti-inflammatory Activities of the D-P in Eastern Mediterranean region.

Testing Method, Results and Reference/s
Arum palaestinum
Leaves were extracted with 96% aqueous ethanol, and extract was used to treatcarrageenan-induced paw edema in albino rats. Extract was given orally (200-300 mg/kg b.wt.) and the effect was very weak. [15] 80% Aqueous methanolic leaves extract was prepared and used to treat UVB-irradiated (2 J/cm^2) human cultured skin. Concentration of IL-1α was measured and the results show high activity. [16] Inflammation was induced by LPS in human monocytic cell line (THP-1)-derived macrophages, then they were treated with leaves aqueous ethanolic (96% v/v) extract. The treatment significantly suppressed the production of pro-inflammatory biomarkers and increased the production of anti-inflammatory biomarkers. [17]
Cichorium pumilum
Roots were extracted with 95% aqueous ethanol, and extract was fractionized with ethyl acetate (EA). LPS-induced inflammation in rats was treated with the EA fraction (100 mg/kg per day, oral gavage, 7 days), showing high activity. Authors proposed MAPK signaling as mechanism of action, and lactucin (**Figure 2**), isolated from EA fraction, as active natural product. [18] Whole plant was extracted with 70% aqueous ethanol, and extract was fractionized to obtain phenolic acids-rich fraction and three pure acids (**Figure 3**). Injury in mice was induced by injection of methotrexate (**Figure 3**), and animals were treated with the crude extract (100 mg/kg per day, 10 days) and the acids-rich fraction (10 mg/kg per day, 10 days). All five extracts had significant activity, but ferulic acid was most active. [19] Leaves were extracted with 80% aqueous ethanol, and extract was found active against LPS-induced inflammation inTHP-1-derived macrophage M0cells. [20]
Cyclamen persicum
No published studies (see **Discussion**).
Foeniculum vulgare
Dry fruits were extracted with 80% aqueous methanol. Inflammation was induced in mice and rats by carrageenan (paw edema), arachidonic acid (ear edema) and formaldehyde (arthritis). Extract was orally administered (200 mg/kg per day, 10 days), with 0.5%

sodium carboxymethyl cellulose. In the three tests extract was notably active, and best results were recorded after 3 h. [21]

Rats and mice with carrageenan-induced paw edema were treated with fruits essential oil (EO), with doses of 0.05, 0.1 and 0.2 mL/kg, intraperitoneal injection. Comparing with control (Etodolac), EO was most efficient in 0.05 and 0.2 mL/kg. [22]

Ear edema was induced in mice by arachidonic acid. Seeds were separately extracted with 80% aqueous ethanol and water, and both extracts were analyzed for active compounds. Activity was measured by 5-lipoxygenase release inhibition. Both extracts and some components (γ-terpinene, fenchone, *trans*-anethole, **Figure 4**) were notably active. [23]

Inflammation in rats was induced by injection of cyclosporine. Then, animals were fed with seeds (17 g/kg per day, 45 days), and various inflammatory biomarkers were tested. Treatment resulted significant effect compared with control. [24]

Rats and mice were subjected to inflammation induction by carrageenan (paw edema), acetic acid (writhing) and formaldehyde (paw licking). The three cases were treated with seeds ethanolic extract, resulting positive effect in all of them. [25]

LPS-stimulated inflammation in RAW 264.7 macrophage cells, and they were treated with 80% aqueous methanol fruits extract (100 µg/mL). Several inflammation biomarkers were tested resulting significant improvement. [26]

5-Lipoxygenase (5-LOX) assay was used to test the activity of fruits commercial EO, resulting significant inhibition. [27]

Fruits were extracted with 70% aqueous ethanol and fractionized with several solvents. Dichloromethane fraction treated LPS-induced inflammation in RAW 264.7 macrophage cells. Effect was observed by measuring several inflammation biomarkers. [28]

Inflammation in mice was induced by LPS and the animals were treated with fruits EO (250 µL/kg), resulting improvement of several inflammation biomarkers. Authors propose ERK signaling (extracellular signal-regulated kinase) as a possible mechanism of action. [29]

Aqueous extract of seeds was prepared, and it was used in ointment (2% and 7%) to treat formaldehyde-induced inflammation in rats. After 16 days, the 7% ointment reduced inflamed area by 91%, while 2% preparation effect was 81% and standard (mupirocin) 92%. [30]

Fresh leaves 50% aqueous methanolic extract was active against inflammation in THP-1-derived macrophagecells. [31]

A solution (100 g in 400 mL of water) of dry aqueous seed extract, was administered (0.8 mL/kg per day, 4 days) to rat puppies with necrotizing enterocolitis ($CO_{2\ (g)}$ inhalation). Testing several biomarkers showed positive effect of the treatment (puppies were scarified). [32]

Dry fruits and leaves were extracted with 96% aqueous ethanol, and extract was orally administered to rats with carrageenan-induced inflammation: 87.5, 175 and 350 mg/kg. All doses showed positive effect. [33]

95% Aqueous ethanol seeds extract had significant effect against LPS-stimulated inflammation in RAW 264.7 macrophage cells. [34]

Fruits EO was prepared by using *n*-hexane as collecting solvent, and GC-MS analysis found estragole as major component (**Figure 5**). Inflammation in neutrophils that were isolated from human blood, was induced using the fMLF/CB superoxide generation (N-Formymethionyl-leucyl-phenylalanine, **Figure 5**), and it was treated with EO. Positive effect was measured by several biomarkers, and authors propose blocking of Ca^{+2} from Gi-protein to MAPKs (mitogen-activated protein kinases) by estragole, as mechanism of action. [35]

Seeds were extracted with ethanol/CO_2 and extract was active against carrageenan-

induced paw edema in rats. [36]
Seeds EO was active in 5-LOX inhibition assay. [37]
Plant waste was analyzed for active phytochemicals. Six phenolic acids were identified, and the active anti-inflammatory (inhibition of COX-1 and COX-2) compounds were kaempferol, isorhamnetin, andquercetin glucuronide (**Figure 6**). [38]
Aerial parts, including fruits, were separately extracted with *n*-hexane, methylene chloride, ethyl acetate and methanol. All extract showed positive effect on carrageenan-induce paw edema in rats, and methanol extract was most potent. In this study, comprehensive chemical compositions of extracts were determined. [39]
R-(+)-Limonene (**Figure 7**), a major ingredient of seeds EO, and fenchone (**Figure 4**), were commercially purchased and applied for wound healing in rats. Both compounds had anti-inflammatory activity by increase of collagen synthesis. [40]
Pure commercial *trans*-anethole (**Figure 4**) had anti-inflammatory activity against LPS-induced lung injury, by regulation of Th17/Treg (T cell helper 17, T cell regulatory) function. [41]
Pure coumarins (**Figure 7**) isolated from fruits, were active against LPS-induced inflammation in RAW 264.7 microphages and in a TPA-stimulated mouse model of skininflammation (TPA, 12-O-tetradecanoylphorbol-13-acetate). [42]

Gundeliatournefortii

Aerial parts were extracted with 95% aqueous ethanol, and extract was active against edema induced in mice by formaldehyde (paw) or xylene (ear). [43]
Inflammations was separately induced in rats by acetic acid, formaldehyde, and hot plate. Theses were treated with aerial parts EO, resulting positive effect in the three cases. Chemical composition of EO was determined, and major components are shown in **Figure 8**. [44]
Aerial parts were burned and mixed with milk to prepare an ointment. This was applied on second degree burns in rats, resulting significant decrease of burns. [45]
Aqueous extract of flowering buds was prepared and used to treat inflammation caused by implanted hepatocarcinoma cells in mice (reduction of F4/80 count). [46]

Majorana syriaca

Aerial parts EO was prepared and analyzed with GC-MS for chemical composition. Major compounds are shown in **Figure 9**. EO had activity against LPS-induced inflammation in RAW 364.7 microphages, tested by inhibition of NO production. [47]
Three acids (**Figure 10**) known for their anti-inflammatory activity (LPS-induced inflammation in RAW 364.7 microphages) were isolated and quantified by LC-MS, from the aerial parts ethyl acetate extract. [48]
Aerial parts 90% aqueous ethanol extract was prepared and found active against carrageenan-induced paw edema in rats. [49]
Methanolic leaves extract was suppressed the release of cytokine IL-6 but not cytokine IL-10 in human peripheral blood mononuclear cells. [50]
Aqueous and *n*-hexane leaves extracts were separately prepared. Extracts were used to treat (50 mg/kg per day, 10 days, intraperitonealadministration) mice were infected with *Schistosoma mansoni*. Both extracts had positive effect. [51]
Follow-up (ethanolic extract) of previous study using scanning electron microscopy. This study focused on *M. syriaca*. [52]
Leaves 70% aqueous ethanolic extract inhibited 5LOX, COX-1 and $sPLA_2$-Venzymes. [53]

Malva sylvestris

80% Aqueous methanolic leaves extract was prepared and used to treat UVB-irradiated (2 J/cm^2) human cultured skin. Concentration of IL-1α was measured and the results show

low activity. [16]
Flowers were extracted with diethyl ether, and 200 mg/kg of it were used to treat wounds in alloxan-induced diabetic rats. Treatment reduced wound area by collagen production and inhibition of inflammation. [54]
Follow up of previous study: flowers chloroform extract, same dose, healthy rats. Wound healing and anti-inflammatory activities were higher. [55]
Leaves were extracted with 96% aqueous ethanol, and extract was analyzed with LC-MS to obtain scopoletin, quercetin and malvidin-3,5-glucoside (**Figure 11**). The crude extract and the three compound were used to treat TPA-induced ear edema in mice. Extract (0.2 mg/ear) and malvidin-3,5-glucoside (0.05 µmol/ear) were active. [56]
70% Aqueous ethanolic leaves extract was mixed (20%) with Orabase, and the resulting ointment treated wounds in rats. Wound area was decreased, and inflammation progress was inhibited, compared with control. [57]
Leaves were extracted with ethanol and the extract was fractionized with chloroform. Both extract and fraction had significant anti-inflammatory activity against *Aggregatibacteractinomycetemcomitans*-infected human oral cells. Activity was expressed by down regulation of inflammatory genes. [58]
A cream contains 1% flowers aqueous extract, had wound healing and inflammation preventive activities in mice. [59]
Aerial parts were separately extracted with water, ethanol, and *n*-hexane, and from the aqueous extract, a polysaccharide was isolated and characterized. Aqueous extract and polysaccharide had significant activity of preventing inflammation in acetic acid-induced ulcerative colitis in rats. [60]
Leaves ethanolic extract was prepared and fractionized with *n*-hexane, chloroform, ethyl acetate and water. Using three inflammation models (*in vitro* and *in vivo*, mice), it was found that only the aqueous fraction had notable activity. [61]
Leaves and flowers ethanolic extract was prepared and fractionized with *n*-hexane, chloroform, ethyl acetate and water. LPS-induced *in vitro* inflammation model was used to test activity of extract and fractions. Release of inflammatory mediators PGE_2, PGD_2, TXB_2, and $PGF_{2\alpha}$ was measured, revealed activity mainly for extract, ethyl acetate and aqueous fractions. Authors propose inhibition of prostanoid production as the mechanism of action. [62]
Three extracts were prepared from leaves: ethanolic, 70% aqueous ethanolic and aqueous. Extracts were tested in postoperative peritoneal adhesionin rats, showing different, but positive effects for all of them. There was low influence on inflammatory biomarkers. [63]
Flowers were extracted with 70% aqueous ethanol, and the same solvent was used to separately extract flowers of *Carum carvi andMedicago sativa*. Each extract was separately tested against formaldehyde-induced paw edema in rats. All extracts were active (600 mg/kg) and the combination of the extracts was most potent. [64]
The 95% aqueous methanol leaves extract was prepared and used to treat ischemia-reperfusion injury in rats (*in vivo*) and in H9c2 cells (*in vitro*). [65]
Aerial parts were extracted with ethanol and fractionized with water. This fraction decreased the release of inflammatory biomarkers, especially IL-6 in HIV infected TZM-b1 cells. [66]
Aerial parts ethanolic extract was used to prepare a topical cream that treated atopic dermatitis in children. [67]
Fruits powder, aqueous and ethanolic extracts were used to treat carrageenan-induced paw edema in rats. All products were active, and the aqueous extracts (100 mg/kg) was most potent. [68]

Leaves ethanolic extract and flowers aqueous extract, were prepared; and ferulic acid (**Figure 3**) was isolated from extracts. The three products were tested against inflammation of wounds in mice, as well as in HaCaT cells. All products were active decreasing release of inflammatory biomarkers (IL-6, IL-1β). [69]

Aerial parts ethanolic extract was used (10%) to prepare a cream for wound healing in humans. There was no significant activity. [70]

Aqueous and acetone extracts of aerial parts were prepared and tested for inhibition of bovine serum albumin denaturation. Aqueous extract was more active than acetone extract, but less than control, diclofenac sodium. [71]

Micromeriafruticosa

Aerial parts were extracted with 80% aqueous methanol, at 80 °C (boiling point 82.5 °C). The extract was tested in three concentrations (20, 40, 60 µg/mL) for inhibition of *in vitro* oxidation of 3,3',5,5'-tetramethylbenzidine by MPO/H_2O_2/Cl^- system (MPO, myeloperoxidase). The concentration of 60 µg/mL was most active with 86% inhibition. [72]

Aqueous extract of aerial parts was prepared and tested for anti-inflammatory activity in four models: MPO inhibition, carrageenan-induced paw edema in mice, acetic acid-induced vascular permeability in mice, and indomethacin-induced ulcer in mice. Among three concentrations, 200 mg/kg was most potent. [73]

Salvia fruticosa

Aerial parts were separately extracted with ethanol, chloroform, 1-butanol, and water. Chloroform extract had the highest activity against carrageenan-induced paw edema in rats (25 mg/kg, orally). [74]

Methanolic extract of aerial parts was prepared and tested against LPS-induced inflammation, *in vitro* (RAW 264.7 cells) and *in vivo* (mice). In both cases, inhibition proinflammatory biomarkers production was measured: TNF-α, IL-6 and IL-1β. [75]

Aerial parts were separately extracted with water, methanol, *n*-butanol, acetone, and chloroform. All extracts (including of two other species of *Salvia*) were tested against carrageenan-induced paw edema in rats. *n*-Butanol extract of *S. fruticosa* was most active. [76]

Methanolic extract of aerial parts was found active (500 mg/kg, intraperitoneal injection) against carrageenan-induced edema in mice. [77]

Aerial parts were extracted with 70% aqueous methanol, and the extract was used to treat $AlCl_3$ – induced Alzheimer's disease neuroinflammation in rats. Using 375 or 750 mg/kg, daily for three months, had notable effect of reducing the release of inflammatory biomarkers, including acetylcholinesterase (AChE). [78]

Roots and aerial parts were separately and successively extracted with chloroform, ethyl acetate, methanol, and 1-butanol. The methanolic extracts had the same effect against carrageenan-induced paw edema in mice. [79]

Nanovesicles were loaded (17-66 mg/mL) with leaves EO and were found active in soybean lipoxygenase inhibition assay. Major compounds in this EO are shown in **Figure 12**. [80]

Leaves and flowers were separately extracted with methanol (mercerization) and ultrasound-assisted extraction. Extract was found active against LPS-induced inflammation in RAW 264.7 cells. [81]

Sinapis alba

Mice diet that included 5% seeds,imiquimod-inducedpsoriasiform inflammation on shaved back skin of the animals. [82]

Seeds aqueous extract was active against LPS-induced inflammation in RAW 264.7 cells. [83]

Seeds were extracted with 50% aqueous ethanol. Extract had positive effect on TPA orarachidonic acid or croton oil-induced ear edema in mice. [84]

Figure 2. Lactucin isolated from roots of *Cichorium pumilum* [18]

Figure 3. Active acids from*C.pumilum* against methotrexate injury [19]

Figure 4. Anti-inflammatory natural products from *Foeniculum vulgare* [23]

Figure 5. Estragole from *F. vulgare*, active against fMLF-induced inflammation[36]

Figure 6. Anti-inflammatory natural products isolated from *F. vulgare* waste[38]

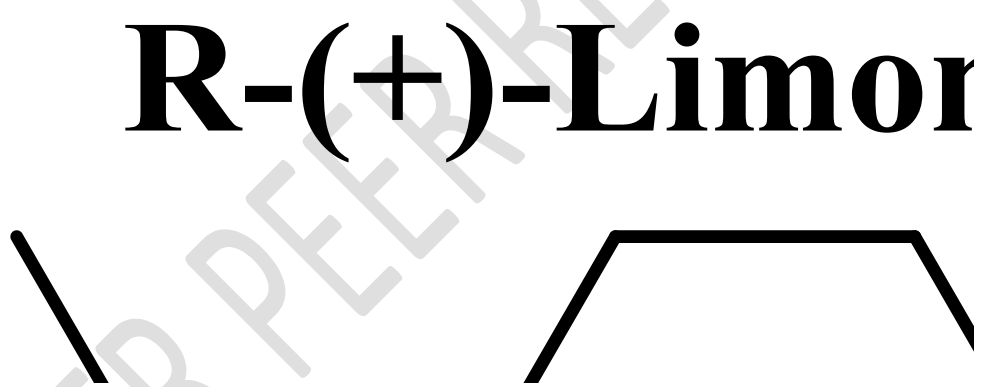

Figure 7. Anti-inflammatory pure natural products foundin*F. vulgare*[40,42]

Figure 8. Major constituents of aerial parts essential oil of*Gundeliatournefortii*[44]

Figure 9. Major constituents of aerial parts essential oil of*Majorana syriaca*[47]

Figure 10. Anti-inflammatory acids from aerial parts ethyl acetate extract of*M.syriaca*[48]

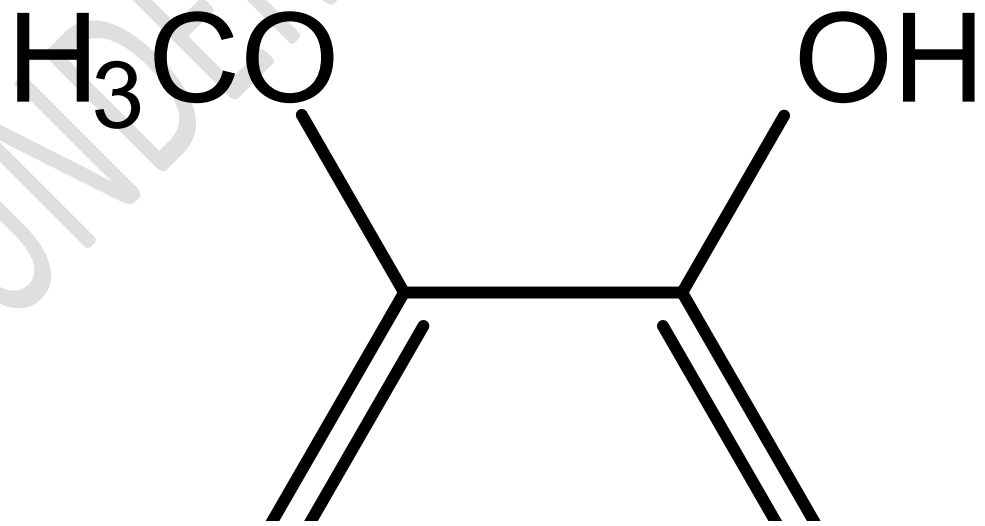

Figure 11. Active compounds from*Malva sylvestris*[56]

Figure 12. Major constituents of leaves essential oil of*Salvia fruticosa*[80]

4. Discussion

The presentation of published modern research results of anti-inflammatory activity of the Deca-plants (D-P) revealed very interesting fact: while some plants were extensively published, others werelimitedly published or not published at all (*Cyclamen persicum*). Another interesting and contradictory reporting was presented about the anti-inflammatory activity of *Arum palaestinum*. Despite being aware of the different testing methods, the reported results of anti-inflammatory activity of the leaves extracts of *Arum palaestinum* according to references 15 (very weak) and 16 (very strong)areeasily notable.The different extracting solvents: 96% aqueous ethanol and 80% aqueous methanol, respectively, does not provide possible explanation since literature reports concerning the efficiency of these solvents are quite contradictory[85-88].

The importance of anti-inflammation research and its findings consistency, arises from the understanding that we already mentioned in the **Introduction**, that inflammation is involved in almost all diseases. To make this statement even more valid, we will present some of the very important recent publications. I.G. Onyango and his colleagues reviewed the relationship between neuroinflammation and Alzheimer's disease: they present a comprehensive view of the causes of neuroinflammation and major known interventions [89]. A. Kurowska and her colleagues, focused on the importance of healthy diet in prevention of inflammatory processes that lead to neurological diseases [90]. This presentation connects directly to our interest in this article about D-P, and it has another advantage: it reviews unhealthy, pro-inflammatory foods and not only anti-inflammatory nutrition.

The recent research of A. García-Sánchez and his colleagues proved a direct relationship between inflammation and obesity and hypertension [91]. For example, in normal-weighthuman subjects of the research, the concentrations of pro-inflammatory cytokines were 206.4 pg/mL for TNF-α, and 63.9 pg/mL for IL-6. For overweight and obese subjects, concentrations were 195.6, 66.5 and 496.2, 217.0 pg/mL, respectively.Following the previous findings, D. Moriki and her colleagues found clearnegative linkage between adherence of anti-inflammatory diet and atopic diseases prevalence, as shown in **Table 2** [92].

Table 2. Adherence to an Anti-Inflammatory dietand atopic diseases prevalence among Greek youngsters [92]

Adherence to an Anti-Inflammatory diet	Low	Moderate	High
Asthma symptoms in the past 12 months (%)	10.8	8.3	4.6
Allergic rhinitis symptoms in the past 12 months (%)	29.2	24.7	24.5
Allergic rash symptoms in the past 12 months (%)	8.9	9.5	8.5
Overweight/Obese (%)	33.0	31.6	32.6

To conclude this part, we will cite the comprehensive review article of F. Stumpf and her colleagues [93]. They presented the benefits of healthy diet as strong anti-inflammatory factor, and the unhealthy and pro-inflammatory nutrition, like in the review article of A. Kurowska and her colleagues [90]. But the article of F. Stumpf *et al*. also reviewed the role of malnutrition in inflammation.

Three studies have reported anti-inflammatory activity of *A. palaestinum* [15-17], but none of them linked this activity to specific natural products (NPs) contained in this plant.In a very detailed study, I.M. Abu-Reidah and his colleagues, have published the chemical composition of *A. palaestinum* [94].Carefully studying the list of compounds that they presented, shows that there are at least two natural products with known and published anti-inflammatory activity: laurocapram (azone) and 7-methoxy coumarin[95,96], that their structures are shown in **Figure 13**.

Figure 13. NPs with reported anti-inflammatory activity contained in*A. palaestinum*[92,93]

In section 3 (Anti-inflammatory Activities of the Deca-plants and Their Natural Products), we have cited three studies of anti-inflammatory activity of*Cichorium pumilum* [18-20]. One of them however (19, E.E. Eltamany*et al*.), linked this activity with three phenolic acids (Figure 3). These acids are very widespread in the plant kingdom. But studying the chemical composition of *C.pumilum*, reveals the fact that it contains NPs family, found in some other plants: norisoprenoids[97]. Later studies have shown that two of these NP's, 4 and 5 in **Figure 14**, have notable anti-inflammatory activity [98,99].

Figure 14. Norisoprenoids contained in*C. pumilum*[97-99]

To the best of our knowledge, *Cyclamen persicum* was not published by modern research as having anti-inflammatory activity. Even though the D-P have very few mentions as having such activity in traditional medicine of the reviewed region, *C.persicum*is used treat skin inflammations[10].Moreover, and more important, analyzing the chemical composition of

this plant shows that it contains several compounds, in significant concentrations, with clear and notable anti-inflammatory activity. For example, M. Cornea-Cipcigan and her colleagues, analyzed leaves of flowers of a few *Cyclamen* species, including *C. persicum*. They published their findings in a comprehensive research article showing a high content of carotenoids [100].These compounds are widely reported and reviewed for having anti-inflammatory activity [101].

Another specific and clearer example was the work of H. Ishizaka and his colleagues: the discovered that among the volatile compounds of *C. persicum*, the isomers *E,E*- and *Z,E*-farsenols are present [102], **Figure 15**. These compounds, especially the *E,E*-isomer, have well known anti-inflammatory activity [103,104].

Figure 15.Farsenols, anti-inflammatory NPs, found in*C. persicum*[102-104]

Inhibition of nitric oxide (NO) production is one of the major anti-inflammatory activities [105], and in this context, it was found that 95% aqueous ethanolic tubers extract inhibited the production of NO in LPS-induced inflammation in cancer cells [106]. Interestingly, the authors of this report do not indicate that this activity is anti-inflammatory, and this is the reason we did not mention it section 3.

As we have presented in Table 1 above, the anti-inflammatory activity of *Foeniculum vulgare* is well known and extensively published[21-42]. This clear and notable property is utilized in some indirect and advanced methods.A. Ammara and his colleagues prepared selenium nanoparticles (SeNP) using *F. vulgare*aqueous seeds extract that reduced sodium selenite [107]:

$$Na_2SeO_{3\,(aq)} + F.\ vulgare \text{ aqueous seeds extract}_{(aq)} \rightarrow SeNP_{(s)}$$

These SeNP had activity against collagenase type II-inducedpaw arthritis in mice.

Z.T. Gias and her colleagues tested the biological activities of a commercial formulation (Panch Phoron) that is composed of: *Foeniculum vulgare*(fennel), *Trigonella foenum-graecum* Linn (fenugreek), *Nigella sativa* (black cumin), *Cuminum cyminum* (cumin) and*Brassica nigra* (black mustard) [108]. They found that this formulation has three inflammation-related activities in mice: antinociceptive, anti-inflammatory andanalgesic.

M.R. Loizzoand her colleagues reported that EO of the leaves of *Majorana syriaca* hadactivity against LPS-induced inflammation in RAW 364.7 microphages, tested by inhibition of NO production [47]. They analyzed this EO by GC-MS and found that Carvacrol, thymol, p-cymene and 2-isopropyl-1-methoxy-4-metylbenzene (Figure 9) were the major constituents, but they did not link the anti-inflammatory activity to all or some of these compounds.

In terms of chemical composition of the EO of *M. syriaca* leaves, the report of M.R. Loizzo*et al*. is consistent with previous reports such as of S. Abu-Lafi and his colleagues [109], where carvacrol and thymol were major ingredients. Several publications have reported the notable anti-inflammatory activity of these compounds[110,111].

Malva sylvestris is one of the most studied, published, and reviewed plants [for example, 112-114]. In our presentation, we have cited 19 publications of the anti-inflammatory activity of this plant [16,54-71]. Phenolic compounds are among the top anti-inflammatory NPs contained in *M. sylvestris*, and malvidin-3,5-glucoside is the most active (Figure 11), [56]. These results are consistent with other published studies about the anti-inflammatory properties of malvidin and its derivatives [115]. But none of the 19 studies that we cited, indicated delphinidin, a phenolic compound contained in *M. sylvestris*[116], and possesses high anti-inflammatory activity [117].

In section three, we cited 8 publications about the anti-inflammatory activity of *Salvia fruticosa*[74-81], andin Figure 12 we presented the major components of *S. fruticosa*leaves EO, that has anti-inflammatory activity.[80]. But this plant contains high concentrations of rosmarinic acid [118] (Figure 10), which also have strong anti-inflammatory activity [48,119,120].

Another phenolic acid contained in *S. fruticosa*leaves [118], with proven anti-inflammatory activity is salvianolic acid B [121], which also was not mentioned in all the articles we cited about this plant. The structure of this acid is shown in **Figure 16**.

Figure 16.Salvianolic acid B, anti-inflammatory agent found in*S. fruticosa*[118,121]

None of the three articles that we cited about the anti-inflammatory activity of *Sinapis alba* [82-84], mentioned, not to say presented, active anti-inflammatory NPs that this plant contains. The chemical composition of this plant was studied and published:seeds EO [122-124], seeds *n*-hexane extract [125], and a very recent, very comprehensive, andvery detailed composition that was achieved by several extractions and fractionations [126].

Carefully studying the lists of compounds in the last four cited publications [122-126], reveals the fact that many of these NPs have known and published anti-inflammatory activity. Here we will present the most studied and published, and they are presented in **Table 3** and **Figure 17**.

Table 3. Selected Anti-Inflammatory Compounds in *Sinapis alba*

Compound Name	Testing Method/s [Reference]
Allyl isothiocyanate	LPS-induced neuroinflammation [127]
Benzyl isothiocyanate	LPS-induced inflammation in RAW 264.7macrophages and TPA-induced ear enema in mice [128] Indomethacin-induced gastric injury [129]
Genipin	Croton oil-inducedear edema in mice [130]
Geniposide	Wound healing in diabetic rats [131]
Glucoraphanin	LPS-induced inflammation in THP-1 cells [132]
Sinapic acid	Carrageenan-induced paw edema in rats [133]
Sinapine	Fatty liver inflammation in mice [134]
Sulphoraphane	LPS-induced inflammation in RAW 264.7 cells and in mice [135] LPS-induced inflammation in human dendritic cells [136]

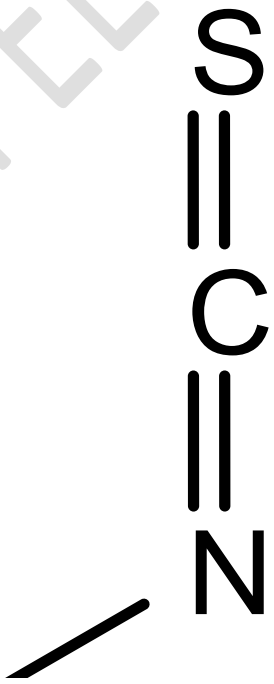

Figure 17.Selected anti-inflammatory NPs found in*S. alba*[127-136]

5. Selected Wild Edible Non-Deca-Plants with Anti-inflammatory activity

The plants, subject of this review article that we named as Deca-plants (D-P) are the most consumed edible wild plants in Eastern Mediterranean region. This last statement is not based

on scientific reports, but rather personal knowledge of the author, and it is highly correct for the region between Eastern Mediterranean shores and the Jordan river.

But peoples of the smaller or the greater reviewed regions, eat dozens of other wild plants, obviously, as well as dozens of cultivated plants. Among the edible wild plants that are not included in the D-P (N-D-P), some compete with the D-P plants in the extent of consumption, such as *Malva nicaeensis*, that is eaten like *Malva sylvestris*, and in hilly areas even more. Some of these N-D-P, possess notable anti-inflammatory activity. In **Table 4** we present eight of these plants, the most common ways of their consumption, and selected reports of their anti-inflammatory activity.

Table 4. Selected Wild Edible Non-Deca-Plants with ReportedAnti-InflammatoryActivity

Plant Name	**Main Method/s of Consumption [Anti-inflammatory Report]**
Capparis spinosa	Pickled buds [137]
Malva nicaeensis	Cooked or fresh in salads (like *M. sylvestris*) [138]
Matricariaaurea	Herbal drinks [139]
Notobasissyriaca	Peeled young stems eaten fresh, seeds as coffee substitute [140]
Portulaca oleracea	Fresh in salads, cooked or in omelets [141]
Rumex acetosa	Pastry filling (like *Spinacia oleracea*, Spinach) or fresh[142]
Salvia hierosolymitana	Leaves stuffed with rice (like stuffed grape leaves) [143]
Urtica urens	Young stems eaten fresh, in salads or cooked [144]

6. Conclusions

1) The top ten most edible wild plants (Deca-plants, D-P) of Eastern Mediterranean region have notable anti-inflammatory activities.

2) Some of the D-P were limitedly studied and/or published, and there is a need to investigate the anti-inflammatory activities of these plants.

3) It is highly important to find the natural products contained in the D-P and are responsible for the anti-inflammatory activities.

4) When these natural products are known, it is important to study the mechanisms of action of their anti-inflammatory activities.

5) It is important to study synergistic effects of active anti-inflammatory D-P products.

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