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Top Edible Wild Plants of Eastern Mediterranean Region. Part IV: Antimicrobial and Antiviral Activities.

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ABSTRACT

In the first three parts of this series of review articles, we presented the anticancer, anti-inflammatory and antidiabetic activities of the most important (eaten) wild edible plants of eastern Mediterranean region, which we named as the “Deca-plants” (D-P). In this review article, we will present the antibacterial, antifungal, and antiviral activities of these very important plants. The D-P published literature of these activities is vast, with large differences between the species. Moreover, in most articles there are reports of the chemical compositions of the plant parts, extracts or essential oils (EO). These compositions are very interesting, but we will present only small part of them, otherwise, this article could be very long. Special attention will be given in the introduction to antibiotics resistance and its consequences. To provide an almost comprehensive and comparative presentation, in the last part of this article, selected Non-Deca-Plants with reported antibacterial/antiviral activity will be shortly reviewed, when the criteria of selection are wild and edible.

Keywords: antibacterial, antiviral, infectious diseases, MIC, inhibition zone, antifungal, antibiotics resistance, plant extracts, essential oils, hydrodistillation.

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INTRODUCTION

Microorganisms and viruses are present around, on and inside human body ever since. Some of the bacteria that live in the human body and often named microbiota, are very important for health of humans [1], but in this review article, we will discuss only harmful bacteria and viruses.

Harmful bacteria and viruses had their adverse effect on humans since the dawn of humanity. Archeological research found this effect in humans remains from ancient Egypt [2]. Among the most important examples we can find plague, or “black death” caused by *Yersinia pestis* bacterium [3]. And the eruption of plague in central Eurasia during the 14th century, is considered one of the worst pandemics in human history [4]. And in our times, the most recent example is COVID-19 pandemic caused by various mutation of the Corona virus. According to the World Health Organization (WHO), has claimed 6.9 million victims until last week of September 2023 [5]. In addition to major viral pandemics (Swine flu, Bird flu, Ebola) outburst in the last 50 years, influenza virus kills around 470000 humans, in average, every year [6].

The fight between humans and bacteria had a turning point after its discovery by A. van Leeuwenhoek in 1677 [7]: the race for antibiotics turned into systematic science. The same thing can be said about the development of antiviral agents, that reached a milestone after the discovery of viruses by D.I. Ivanovsky in 1892 [8].

Many researchers consider the production of atoxyl (**Figure 1**) by A. Béchamp as the first synthesis of antibacterial or antibiotic agent, even though, the active compound is arsanilic acid (**Figure 1**) and not its sodium salt, atoxyl [9].

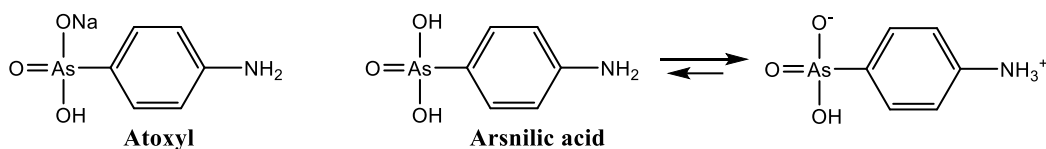


Figure 1: Atoxyl and arsanilic acid which is considered the first antibiotics [9]

The success of antibiotics was tremendous in reduction of mortality rates caused by infectious diseases [10]. But with this success, three major challenging outcomes emerged: antibiotics resistance of the bacteria, adverse effects of the antibiotics and removal of antibiotics waste from the environments, especially water sources. The third problem will be presented in the **Discussion** section.

Antibiotic resistance was defined in several ways, but it can be said that it is the ability of a microorganism to survive and/or grow certain concentration of antibiotic agent, which is usually effective for killing or inhibition of the same species [11]. And consequently, antibiotic resistance is one of major threats to humanity [12]. Antibiotic resistance is developed by various factor, where genetic changes and mutations in the bacteria is on the top of them [13]. But bacteria take one or more of the following actions that result in antibiotic resistance [14]. Blocking the entrance of antibiotic to the bacteria cell; expelling the antibiotic from the cell; inactivation of the antibiotic by changing its structure or degradation; and, changing the antibiotic target within the bacterium cell. Another important aspect of antibiotics resistance is the fact that some bacteria developed multidrug resistance, meaning that they are immune to several types of antibiotics [15].

Adverse or negative side effects of antibiotics use were studied and published by many researchers. P.D. Tamma and her colleagues found that at least 20% of antibiotics users experienced antibiotic-associated adverse drug events, ADEs [16]. These ADEs included diarrhea, nausea and vomiting, hematologic event, hepatobiliary effects, renal complications, dermatologic problems, cardiac effects, severe allergies (anaphylaxis) and muscle inflammations (myositis). S. Shekhar and F.C. Petersen name antibiotics “unavoidable drug” but they found that it has adverse effect on immune system of infants [17]. K. Dinan and T. Dinan warn of focusing on antibiotic-resistance while developing new antibiotics, since these might have adverse effect on brain-gut-microbiota, as they have summarized in their review article [18].

To provide more focused image of the adverse effects of antibiotics, we will give as examples two of the most frequently used in a global scale: amoxicillin and doxycycline [19]. The structures of these compounds are shown in **Figure 2**.

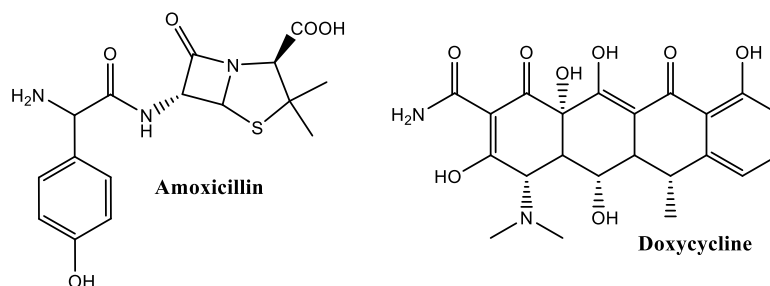


Figure 2: Amoxicillin and doxycycline, two of the most frequently used antibiotics [19]

M. Gillies and his colleagues summarized the adverse effects of amoxicillin in a review article, and these included: nausea, vomiting, diarrhea, candidiasis and rash [20]. N.E. Holmes and P.G. Charles reviewed the negative side effects of doxycycline, and their major findings were: gastrointestinal (nausea, vomiting, diarrhea and epigastric burning), dermatological (photosensitivity and photo-onycholysis), bones and teeth (discolouration of teeth, reduction in fibular bone growth) [21].

In addition to the mentioned above major issues that are part of antibiotics use, it is important to take into account the economic burden of this use: from USD 21.1 to 34.8 billion, between 2000 and 2015 [22]. For these reasons and the problems of treating antibiotics hazardous waste (**Section 4**), it is highly important to replace synthetic antibiotics with natural products.

The use of medicinal plants started with human existence, and the earliest recorded use dates into the Sumerian era, around 5000 years before our time [23]. The Ebers Papyrus of ancient Egypt that dates from approximately the same time, listed 700 plant-based drugs, including gargles, pills, infusions and ointments [24]. The knowledge of traditional medicines that was achieved during 5 millennia, proved to have significant scientific basis when tested for antibacterial activity [25]. Moreover, screening publications about plants with proven activity against antibiotic resistant bacteria, yields a list of more than two dozens, about a decade ago [26]. Few years later, the mechanisms of action of plant-based products that treated antibiotic resistant bacteria became more and more clear [27]. And recently, there is increasing knowledge of the active natural products (NPs) that are responsible for this crucial activity [28].

Finally, the D-P 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).

Ethnomedicinal Antibacterial and Antiviral Activities of the Deca-Plants

Despite the fact that bacterial and viral diseases existed along with humans, ethnomedicinal practitioners did not know the cause of these diseases: bacteria and viruses. They treated infectious diseases with plants in the same way they treated other illnesses [29,30]. But in the written or unwritten knowledge of traditional medicines, there is no evidence that healers knew that these diseases were caused by microorganisms and viruses.

Antibacterial and Antiviral Activities of the Deca-Plants and Their Natural Products

Modern science has acknowledged the great potential of the D-P as antibacterial and/or antiviral, so we found many published articles. In a very few cases, we chose not to cite some articles, since their finding and/or their methods seemed unreliable. A summary of modern science of antibacterial and/or antiviral activities of the D-P is presented in **Table 1**.

Table 1: Antibacterial and Antiviral Activities of the D-P in Eastern Mediterranean region.

| Testing Method, Results and Reference/s |
|---|
| <p><i>Arum palaestinum</i> The aim of this study was to find correlation between radical scavenging (antioxidant) and antibacterial activities. Values of antioxidant activity are listed while values of antibacterial activity are only presented in a not so clear graph. Leaves were extracted with water or methanol (polar extracts) and ethyl acetate or <i>n</i>-hexane (nonpolar extracts). For polar extracts, a vague negative correlation was found and for nonpolar extracts, a vague positive correlation was found. [31] Flowers aqueous extract was tested against <i>P. vulgaris</i> and <i>E. faecium</i> and MIC (minimum inhibitory concentration) values were 6.25 mg/mL for both bacteria. Ampicillin was used a reference, MIC=18 mg/ml, respectively. Ampicillin has very similar structure to amoxicillin but has no hydroxyl group on the aromatic ring. [32] Identical to the previous work. [33] Leaves were separately extracted with water and CH₃OH/CH₂Cl₂ (1:1, v/v), and both extracts were tested against four bacteria strains. Very weak effect for both extracts. [34] Leaves were extracted with 70% aqueous ethanol, and extract had strong activity against several bacterial strains. [35] Methanolic leaves extract and its major components (GC-MS, Gas Chromatography Mass Spectrometry) were tested against corona virus proteins, 3CL^{pro} and Nsp15. Among 19 compounds, β-sitosterol, androstan-3-one, phenobarbital, maltose, and α-tocopherol (Figure 3), had the strongest binding. [36]</p> |
| <p><i>Cichorium pumilum</i> Leaves extracts. See detailed description for his reference in <i>Arum palaestinum</i>. [31] Aqueous and ethanolic extracts were prepared from callus grown from leaves. Aqueous extract had very weak activity against several gram-positive and gram-negative bacteria, while ethanolic extract showed notable activity. [37] Seeds, roots and leaves were combinedly extracted with water, methanol and chloroform (3 extracts). Extracts were tested against: <i>S. aureus</i>, <i>B. cereus</i> (gram-positive), <i>S. typhimurium</i>, <i>E. coli</i> (gram-negative), <i>C. Albicans</i>, <i>A. niger</i> (fungi). Aqueous extract was most active against bacteria and methanolic extract was most active against fungi. [38] Aerial parts were extracted with 80% aqueous methanol, and extract showed moderate activity against some of 19 tested fungi species. [39] Follow-up of previous study. Similar results. [40] Leaves aqueous extract was tested against three <i>Aspergillus</i> spp: <i>A. flavus</i>, <i>A. ochraceus</i> and <i>A. parasiticus</i>. It had no effect against first fungus but had strong activity against the second and the third fungi. [41] Shoots were separately extracted with 70% aqueous ethanol, methanol, acetone and water. All extracts were tested against two fungi species: <i>A. ochraceus</i> and <i>A. alfatoxiformans</i>. Methanolic extract had highest inhibition activity. [42]</p> |
| <p><i>Cyclamen persicum</i> Leaves extracts. See detailed description for his reference in <i>Arum palaestinum</i>. [31] Tubers were separately extracted with water, methanol, ethanol and <i>n</i>-hexane. All extracts were tested against two species of gram-positive and two species of gram-negative bacteria. Only methanolic extract had significant activity and only against gram-positive bacteria. [43] Tubers were separately extracted with water, methanol, ethanol and acetone. All extracts were tested against 5 gram-positive bacteria species, 7 gram-negative bacteria species and 4 <i>Candida</i> species (antifungal activity). Except for aqueous extracts, organic extracts were very active in the three tests. In this study, hyptatic acid-A (Figure 4) derivatives isolated and characterized. [44]</p> |
| <p><i>Foeniculum vulgare</i> Leaf and stem extracts. See detailed description for his reference in <i>Arum palaestinum</i>. [31] Aerial parts EO was prepared by hydrodistillation and tested against 25 bacteria species. It was active against all bacteria, where the highest activity was against <i>C. perfringens</i>. EO was analyzed by gas chromatography (GC) and the three major ingredients are shown in Figure 5. [45] Six compounds (Figure 6) were obtained by analysis of stems methanolic extract, and were tested for antibacterial (<i>E. coli</i>, <i>B. subtilis</i>) and antifungal (<i>A. niger</i>, <i>C. cladosporioides</i>) activities. All compounds were active and scopoletin was most potent. [46] Fruits EO was prepared by hydrodistillation, tested against 29 bacteria species, and found active against most of them. The chemical composition of this EO was analyzed (GC-MS) and the major components were: linalool, <i>p</i>-cymene, α-pinene (see Figure 5) and nerol (Figure 7). [47]</p> |

Seeds EO was prepared and tested against several *Streptococcus* mutants and found active. Authors refer this activity to the major component of this EO: *E*-anethole. [48]

Aerial parts EO was prepared and tested against 30 bacterial strains and found active against all of them. Major components of this EO were: *trans*-anethole (64.08%), α -phellandrene (14.54%), and α -pinene (9.38%). [49]

Seeds EO and methanolic and ethanolic extracts were prepared and tested against 10 bacteria species. The three materials were active, but EO was more potent. Major component of EO was *trans*-anethole, while the major components of the alcoholic extracts were fatty acids: linoleic, palmitic and oleic (**Figure 8**). [50]

Seeds aqueous and acetone extracts were prepared and found active against 11 bacteria species. General chemical compositions were determined. [51]

Seeds EO and methanolic, 80 aqueous methanolic, ethanolic and 80% aqueous ethanolic extracts were prepared. The five materials were tested against 5 bacteria strains, and only EO was active. Major components of EO were (%): *trans*-anethole 68.1, fenchone 9.50, estragole 4.92 and limonene 4.50. [52]

Seeds EO was prepared and tested against 10 bacteria strains. EO had excellent activity compared with synthetic drugs tetracycline (**Figure 9**) and rifampicin. Major components of this EO were: estragole (see **Figure 5**), limonene and fenchone (**Figure 9**). [53]

EO's of aerial parts and seeds were separately obtained by hydrodistillation, and none or very weak activity was recorded against several bacteria species. [54]

Aerial parts EO and *n*-hexane extract were prepared, and both were found against several bacterial strains. *E*-anethole was the major component of EO and extract. [55]

Seeds were extracted with 80% aqueous ethanol, and extract was active against *S. aureus*, *B. subtilis*, *E. coli* and *S. typhi*. MIC values were (mg/mL): 6.4, 12.8, 3.2 and 6.4. [56]

Aerial parts DCM:Methanol (1:1, v/v) extract was prepared and found active against 9 bacteria species (DCM, dichloromethane). Analysis of the extract yielded 7 known compounds (**Figure 10**) that were isolated from this plant for the first time. [57]

EOs were obtained by hydrodistillation from fruits of three organically cultivated cultivars: var. *vulgare*, var. *azoricum* and var. *dulce*. There were no significant differences in antibacterial activity of the three cultivars. Analysis of the three EOs revealed clear differences: in var. *vulgare*, estragole was the major component, while in the other two cultivars, *E*-anethole was the major component. [58]

Leaves EO was obtained with hydrodistillation and had very strong activity against 14 bacteria species, gram-positive and gram-negative. Major ingredients of this EO were previously mentioned, in addition to thymol. [59]

Stems and leaves were extracted with *n*-hexane and analyzed for chemical composition. The extract and the components had low activity, but one compound had moderate activity, 5-hydroxyfuranocoumarin, the demethylation product of bergapten shown in **Figure 6**. [60]

Leaves EO was produced by hydrodistillation and analyzed for chemical composition. It had very strong activity against several bacteria and fungi species. [61]

Seeds were extracted with 80% aqueous methanol, and extract had mild activity against four bacterial strains. Analysis of extract revealed the presence of five major phenolic compounds shown in **Figure 11**. [62]

Seeds were separately extracted with methanol, ethanol, diethyl ether and *n*-hexane, and extracts were tested against several bacteria and fungi species, showing concentration dependent moderate activity. Extracts were analyzed for chemical compositions where polar extracts contained mainly phenolics and fatty acids, while the nonpolar extracts contained mainly oxygenated monoterpenes. [63]

Seeds were hydrodistilled and the resulting EO was tested against 7 bacteria species. It was active against all of them, but there were clear differences in MIC measurements (mg/mL): from 0.125 for *S. Dysenteriae* to 0.25 for *E. coli*. The major components of this EO were: *E*-anethole (68.53%) and estragole (10.42%). [64]

Seeds EO was obtained by steam distillation and it was tested against 36 antibiotics-resistant bacteria species that were isolated from human patients urine. The activity was compared with 7 standard, known antibiotics, and it was moderately active against most of them. [65]

EOs were prepared from fruits taken from 6 different localities in Portugal. Analysis of these EOs showed differences in their chemical composition, mainly the percentages of major components. The antibacterial (9 species) and antifungal (6 species) were approximately the same. [66]

Seeds EO was produced by hydrodistillation and was active against 6 bacterial strains. This EO its major components (**Figure 12**) were (%): 9-octadecenoic acid (18.56), *o*-benzene dicarboxylic acid (14.47), 1,3,3-trimethyl-2-vinyl-1-cyclohexene (10.77), 1H-benzocycloheptene (10.71). [67]

Fruits EOs of 23 samples of the plant from Iran and Europe were obtained by hydrodistillation, and tested against *E. coli*, *S. typhimurium*, *B. subtilis*, and *S. aureus*. Excellent results (MIC) were recorded, especially against *E. coli*: 31.5 µg/mL. *trans*-Anethole was the major ingredient of these EOs. [68]

Seeds methanolic extract was active against several bacteria species. General chemical composition was determined in this study. [69]

Aerial parts EO was obtained by hydrodistillation, and tested against several bacteria strains, showing good activities. *E*-Anethole was the major ingredient of this EO. [70,71]

Commercial EO from aerial parts (hydrodistillation) of organically grown plants had moderate activity against *L. innocua* and *P. fluorescens*. Major components of this EO were limonene, fenchone and *E*-anethole. [72]

EOs were obtained by hydrodistillation from seeds of three organically cultivated cultivars: var. *vulgare*, var. *azoricum* and var. *dulce*. There were no significant differences in antibacterial (4 species) and antifungal (2 species) activities of the three cultivars. Analysis of the three EOs revealed clear differences: in var. *vulgare*, estragole was the major component, *E*-anethole in var. *azoricum* and limonene in var. *dulce*. [73]

Seeds were separately extracted with methanol and water, and both extracts were tested against 20 bacterial strains. Aqueous extract had activity against 12 species, while the methanolic extract had activity only against 4 species. [74]

Seeds were separately extracted with methanol and *n*-hexane. Both extracts were tested against four bacteria and two fungi species. In average, methanolic extract was more active (zone of inhibition). [75]

Seeds EO was obtained by hydrodistillation, and tested against three bacteria (*S. aureus*, *E. coli*, *P. aeruginosa*) and three fungi (*A. flavus*, *A. niger*, *M. canis*) species, revealing strong activities (MIC). [76]

Ethanol seeds extract had various notable activity against four bacteria species, in dose dependent tests. [77]

Seeds EO was prepared using steam distillation. It was tested against several bacteria species alone, or in combination with 13 known antibiotics. EO was active alone, but the combinations showed synergistic effect that exceeded the antibiotics effect. [78]

Fixed oil was produced by extracting seeds with *n*-hexane, solvent removal and esterification of the resulting liquid with methanol. It was tested (before esterification) against four bacteria species and one fungus, showing stronger activity than two standard antibiotics: ampicilin and gentamycin. The major constituents of the fixed oil were 9-octadecenoic acid methyl ester and 9,12-octadecadienoic acid methyl ester. [79]

Four EOs were separately prepared by hydrodistillation from seeds, flowers, aerial parts before flowering and whole plant before flowering. All EOs were tested against seven bacteria and three fungi species, showing significant activities in most tests. [80]

Leaves EO was prepared and tested against three bacteria species and a fungus, resulting significant inhibition compared with four known antibiotics. *Trans*-Anethole was the major compound in this EO. [81]

Methanolic and ethanolic extracts of aerial parts were prepared and tested against 8 bacterial species. Compared with 29 antibiotics, extracts showed moderate to weak activities, when ethanolic extract was more potent. [82]

Seeds were separately extracted with water, chloroform, methanol and 80% aqueous methanol. Extracts were tested against four bacteria species, showing the following results: chloroform and aqueous extracts were inactive; pure methanolic extract was more active than 80% aqueous methanolic, but both had weak activity. [83]

EO was prepared by steam distillation of aerial parts, and tested against *Candida albicans*, showing significant activity, in dose dependent experiments. The major components of this EO were: *o*-cymene, α -phellandrene, α -pinene and estragole. [84]

Fruits were hydrodistilled yielding EO with weak activity against two bacteria and two fungi species. Major components of this EO were: *E*-anethole, fenchone and estragole. [85]

EO was prepared by hydrodistillation of aerial parts and was tested against *Streptococcus mutans*, resulting significant activity, compared with EOs of other plants used in this research. *E*-anethole and fenchone were the major constituents of this EO. [86]

Seeds extraction with buffer pH=7 afforded a protein that had activity against 4 bacteria and 4 fungi species. The estimated molecular weight of the protein is 60 kDa, but the structure was not reported. [87]

Leaves were defatted with petroleum ether and separately extracted with chloroform, methanol and chloroform/methanol (1:1, v:v). Leaves EO was also prepared, where *Z*-anethole and estragole were its

major components. The four crude extracts were tested against two bacteria and two fungi species showing weak to moderate activities, and the EO was completely inactive. [88]

Seeds were used to prepare two EOs, by hydrodistillation and by extraction with cyclohexane. Both EOs were tested against 5 bacterial strains resulting high activity for both, and higher for the cyclohexane extract. *E-anethole* and *fenchone* were the major constituents of both EO. [89]

EOs were prepared by hydrodistillation from seeds harvested in 16 different localities in Tunisia. All EOs were tested against six bacteria and two fungi species showing significant activities and similar results for some microorganisms, but notable differences for others. The chemical compositions of the EOs were clearly different in terms of compounds families (i.e., oxygenated monoterpenes) and single compounds (i.e., estragole). [90]

Seed were extracted with hot water and microwave assistance, and the resulting extract was fractionized with *n*-hexane, ethyl acetate and methanol. The three fractions were tested separately and in combination with Augmentin antibiotics (combination of amoxicillin, **Figure 2** and clavulanic acid), against *B. cereus*, *P. aeruginosa*, and *B. melitensis*. The synergistic effect was weak where Augmentin alone was more active than the combination in most tests. [91]

Seeds from three different locations in Iran were hydrodistilled resulting three EOs. These were tested against three bacteria species and a fungus: no significant differences were discovered. The chemical compositions of the EOs were close with major components of *trans*-anethole, *fenchone* and *limonene*. [92]

Seeds EO was prepared by hydrodistillation and found active against six bacterial strains, with varying levels of activities and concentrations. The major compounds of this EO were *trans*-anethole, *fenchone* and *limonene*. [93]

Leaves EO was prepared by hydrodistillation and tested against 8 bacteria species, resulting wide range of activity (MIC), from very weak to very strong. The major constituents of this EO were *p*-cymene (**Figure 7**), *cuminal* and β -pinene (**Figure 13**). [94]

Seeds were extracted with 80% aqueous ethanol. This extract was tested against *E. coli* according to the following procedures: alone, in combination with Nisin (antibacterial peptide isolated from *L. lactis* bacterium) and in combination with sodium diacetate [$\text{NaH}(\text{CH}_3\text{COO})_2$, antibacterial agent]. It was found that the combination of extract with nisin is more potent than each of the materials, separately, but the combination with sodium diacetate had no synergistic effect. [95]

Seeds were hydrodistilled to obtain EO that was tested against several bacterial strains, showing moderate inhibition. The major components of this EO were *trans*-anethole and estragole. [96]

Seeds EO (steam distillation) had significant inhibition of *E. faecalis* (bacterium) and *C. albicans* (fungus). [97]

Leaves aqueous ethanolic (96%) extract had activity against *Pseudomonas aeruginosa*, in concentration dependent inhibition. [98]

Commercial seeds EO was highly active against 4 bacteria and 4 fungi species. Major ingredients of this EO were (%): *E-anethole* (73.6), *fenchone* (6) and *limonene* (5.7). [99]

EO of fresh fruits was prepared by hydrodistillation and was tested against 5 bacteria and fungi species and influenza (H1N1) virus, resulting high activity. Estragole was the major component of this EO (84.5%). [100]

Seeds ethanolic extract was active against *Staphylococcus aureus*. No numerical results presented. [101]

Seeds were separately extracted with methanol, ethyl acetate and benzene, and extracts were tested against *S. aureus*, *S. typhi* and *E. coli*. All extracts showed significant activities, where the benzene extract was most active, in average. [102]

Fruits EO was prepared by hydrodistillation and was tested against four bacteria and two fungi species, resulting excellent (against fungi) to significant activities (against bacteria). *E-Anethole*, estragole and *limonene* were the major components of this EO. [103]

Fresh leaves were hydrodistilled to obtain EO, and was tested against *E. coli*, *B. subtilis*, *P. aeruginosa*, and *C. albicans*, resulting moderate activity. The major ingredients (**Figure 14**) of this EO were (%): *trans*-anethole (41.18), *cis*-anethole (26.49), α -copaene (13.66) and β -phellandrene (5.38). [104]

Fresh leaves were hydrodistilled to obtain EO, and was tested against 6 bacteria species, including biofilm forming, resulting weak activity. The major components of this EO: *trans*-anethole, α -pinene and estragole. [105]

Leaves EO (hydrodistillation) had weak synergistic effect with silver nanoparticles (AgNPs), since the activity of AgNPs is much stronger than EO. The testing was against six bacterial strains. [106]

Seeds were successively extracted with methanol, petroleum ether, acetone and water. The extract was tested against four bacteria species, and compared with four synthetic antibiotics, extract had moderate activities. [107]

Seeds EO was tested against 4 bacteria species, showing significant activity. The major components of this EO: *trans*-anethole, fenchone and estragole. [108]

Seeds (?) methanolic had moderate activity against three microorganisms. The major ingredients of this extract were *E*-anethole, estragole, benzoic acid and fenchone. [109]

Liquid fermentation product of seeds was tested against *S. aureus*, *E. coli* and *S. typhi* showing medium activity. General chemical composition of the liquid is reported. [110]

Stems and leaves EO was obtained by hydrodistillation tested against several bacterial strains, showing moderate activity compared with other EOs tested in this study. The major components of this EO were α -pinene, α -phellandrene and estragole. [111]

Seeds were hydrodistilled to produce EO which was tested against 3 fungal and 5 bacterial species, showing moderate (against fungi) to high (against bacteria) activity. [112]

Seeds EO (hydrodistillation) was prepared and tested against bacterial disease agents *R. radiobacter*, *P. savastanoi* pv. *savastanoi* and *P. savastanoi* pv. *nerri* (pv. stands for pathovar). Activity was moderate compared with other plants that were investigated in this study, and the major compound contained in this EO was *E*-anethole, 82.8%. [113]

EO was obtained by seeds hydrodistillation and was tested against *S. sclerotiorum* fungus, resulting very high activity, both in contact or as volatile form, in concentrations ($\mu\text{g/mL}$) of 1.6 and 0.2, respectively. [114]

Seeds cold press EO was produced and tested against 18 bacteria species and found inactive. Major component of this EO (88.95%) was *trans*-anethole. [115]

Seeds were extracted with 60% aqueous ethanol. This extract was tested against 3 fungi and 6 bacteria species, showing moderate activity compared with positive control (ketoconazole and gentamycin, respectively). It was also tested against HSV and CoxB4 viruses showing moderate effect. *E*-Anethole was the major component of this extract. [116]

Seeds EO was produced by hydrodistillation and tested against six fungi species, showing significant activity (MIC). *trans*-Anethole, α -pinene and fenchone were the major components of this EO. Authors propose that the mechanism of action of this EO is damaging the plasma membrane and inhibit the enzymes of the mitochondria. [117]

Seeds EO (hydrodistillation) and methanolic extract were prepared against 5 strains of plants fungi, resulting high to excellent inhibition, and EO was more potent, in average. The major components of EO were (%): estragole (76.2), α -thujone (9.6, **Figure 17**) and limonene (8.6); and of methanolic extract (ppm, **Figure 17**): cirsiliol (27.1), protocatechuic acid (11.97) and quinic acid (4.7). [118]

Seeds were hydrodistillation afforded EO that had significant activity against potato virus X, tobacco mosaic virus and tobacco ring spot virus. [119]

Seeds EO (hydrodistillation) and acetone extract were prepared and applied against papaya ring spot virus, showing moderate activity, in several concentrations. [120]

Aerial parts were hydrodistilled to produce EO which was tested against two virus and 12 bacteria species. In this study, several active components such as *E*-anethole were tested against the same microorganisms and viruses. For antiviral activity, EO was comparable with pure natural products, but more potent for antibacterial activity. [121]

Seeds were extracted with 70% aqueous methanol, and major compounds isolated from this extract were quercetin (**Figure 11**) and isoquercetin (3-*O*-1- β -D-glucosyl quercetin). These compounds were tested against *Bluetongue virus*, resulting moderate activity for both compounds and higher activity of isoquercetin. [122]

Seeds were extracted with 98% aqueous ethanol. Extract was tested against influenza virus resulting high inhibition (82.8%) in concentration of 300 $\mu\text{g}/\mu\text{L}$. [123]

Aerial parts and bulbs from different locations in Egypt were used to prepare EOs, either by hydrodistillation or headspace. EOs were tested against hepatitis A and C viruses, showing very high activity. In this study, comprehensive chemical compositions were presented, and were compared with chemical compositions from Spain and Holland. *E*-Anethole was the major component of the Egyptian plant sample. In addition, molecular docking simulation of six major components binding to the virus polymerase. [124]

Gundelia tournefortii

Stems extracts. See detailed description for his reference in *Arum palaestinum*. [31]

Bulbs were extracted with methanol and this extract was separately fractionized with *n*-hexane and ethyl acetate. Fractions were tested against five bacterial strains, showing high activity (inhibition zone), compared with tetracycline as positive control. The chemical composition of the ethyl acetate fraction were some free fatty acids but mainly their esters, and *n*-butylspiropentane (**Figure 18**). [125]

Commercial active compounds identified in another research, were purchased and tested against *S. choleraesuis*: *E*-2-dodecenal was most active (MIC = 6.25 µg/mL). There are some issues with this report. Please see **Discussion** section (4). [126]

Stems ethanolic extract was tested against *S. aureus* and *E. coli*, showing moderate activity (MIC, µg/mL, 62.5 and 31.25, respectively). [127]

Aerial parts were successively extracted with chloroform, ethyl acetate, methanol and water. All extracts were tested against 9 bacterial strains and had high activities (inhibition zone), compared with three known antibiotics. EO of aerial parts was also produced by hydrodistillation, and its chemical composition is reported, but it was not tested for antibacterial activity. [128]

Aqueous extracts of leaves and roots were separately prepared, and the EO of combined plant parts was obtained by hydrodistillation. The three materials were tested against 8 bacterial and fungal species, showing significant activity. [129]

Seeds aqueous extract was prepared and tested against 8 bacterial and fungal species, showing significant activity (MIC). Major compounds of this extract were diethyl phthalate, 1-tetradecanol and 1-hexadecene (**Figure 19**). [130]

Methanolic extract of aerial parts had weak activity (MIC) against 13 bacterial species, compared with other plants used in this study and antibiotics of chloramphenicol. [131]

Whole plant methanolic extract was tested in combination with seven common antibiotics, against *E. coli*, resulting clear enhancement of the activities of these antibiotics. [132]

Majorana syriaca

Leaf and stem extracts. See detailed description for his reference in *Arum palaestinum*. [31]

Leaves were extracted with 70% aqueous ethanol, and extract had strong activity against several bacterial strains. [35]

Leaves EO (hydrodistillation) was prepared and tested against bacterial disease agents *R. radiobacter*, *P. savastanoi* pv. *savastanoi* and *P. savastanoi* pv. *nerri* (pv. stands for pathovar). Activity was excellent compared with other plants that were investigated in this study, and the major compounds (**Figure 15**) contained in this EO were (%): carvacrol (79.8), *p*-cymene (8.15) and γ -terpinene (4.7). [113]

EO was obtained by leaves hydrodistillation and was tested against *S. sclerotiorum* fungus, resulting very high activity, both as volatile form or in contact, in concentrations (µg/mL) of 0.3 and 3.2, respectively. [114]

Leaves methanolic extract was tested in combination with seven common antibiotics, against *E. coli*, resulting clear enhancement of the activities of these antibiotics. [132]

Leaves EO was prepared by steam distillation and tested against 13 bacterial strains, resulting high activity (in average), compared with three commonly used antibiotics. The major components of this EO were (%): γ -terpinene (28), carvacrol (27), *p*-cymene (16) and β -caryophyllene (13). [133]

Ethyl acetate leaves extract inhibited the growth of several *Pseudomonas* sp. (moderate) and lactic acid bacteria (significant), on minced and packed yellow fin tuna. [134]

Commercial EO (66.64% carvacrol) had significant activity against *S. aureus*, *S. pneumoniae* and *C. albicans*. [135]

Leaves EO was obtained by hydrodistillation and tested against 3 bacterial and 5 fungal species. Both activities were compared with those of pure compounds isolated from the same EO (major components): thymol, carvacrol, α -terpinene and *p*-cymene. EO antifungal activity matched that of pure compounds, but the antibacterial activity was weaker, despite being very strong. [136]

Aerial parts EO was produced by hydrodistillation and tested against 4 bacterial strains. Compared with six known antibiotics, EO had high activity (MIC). [137]

EO was produced from aerial parts by steam distillation and tested against 4 bacteria and 3 fungi species, showing significant activities. [138]

Whole plants, wild and cultivated in Sinai desert, were hydrodistilled to obtain EOs. These EOs were tested against 4 bacterial and 8 fungal species, resulting significant activity for both, and higher for EO produced from the wild plants. Very notable differences were detected in the chemical compositions. Here are the concentrations of major components (cultivated, wild, %): α -terpinene (1.2, 5.5), *p*-cymene (8.5, 3.9), γ -terpinene (2, 14.3), linalool (0.2, 9.5), 4-terpineol (0.9, 7.7), α -terpineol (0.2, 5.5), thymol (0.4, 31.7), carvacrol (81.4, 3.9). [139]

Leaves methanolic extracts had excellent activity (MIC = 1 mg/mL) against *S. aureus*, *P. aeruginosa*, and *C. albicans*, also compared with other plants used in this study. [140]

Stems and leaves were hydrodistilled resulting EO, that was analyzed for its components. EO and 15 of its components were tested against seven species of gram-negative bacteria. In average, EO had stronger activity than most of its ingredients. The major constituents of this EO were (%): β -myrcene 22, γ -terpinene 5.3, thymol 7.4, *p*-anisaldehyde 7.6 and carvacrol 19.6 (**Figure 20**). [141]

Leaves EO was obtained using microwave-ultrasonic assisted hydrodistillation (MUAHD), and had notable activity against 5 bacterial strains. Major components of this EO were α -terpinene, γ -terpinene, thymol, carvacrol and caryophyllene. [142]

Leaves were hydrodistilled to produce an EO that was tested against 12 bacteria species and *C. albicans*. Compared with commonly used antibiotics, EO had notable activity. [143]

Aerial parts were brought from three localities and EOs were prepared by hydrodistillation and tested against *S. aureus*, *S. Mutans* and *C. albicans*. Results showed strong activity (MIC), with no significant differences between the three EOs. [144]

Leaves (local subspecies, *M. syriaca* ssp. *sinaicum*) EO was prepared and had significant activity (inhibition zone) against four bacteria and a fungus. The major component of this EO (95.37%) was carvacrol. [145]

Commercial EO was applied against several bacterial species grown on cooked chicken meat. This EO was tested separately and in combination with *Rosmarinus officinalis* EO. Compared with a combination of two synthetic antibacterial agents, BHA-BHT (butylated hydroxy anisole, butylated hydroxy toluene, **Figure 21**), each one of the EOs had significant activity, and their combination was more potent. [146]

Leaves and flowers hydrodistillation afforded EO that was tested against three fungal species (*A. niger*, *Penicillium* spp. and *F. oxysporum*), resulting high activity. [147]

Leaves EO was prepared by hydrodistillation and was tested against 6 *Candida* spp., showing notable activity (MIC). Thymol, carvacrol and *p*-cymene were the major components of this EO. [148]

EO was produced by hydrodistillation (plant part/s not indicated) and had significant activity against *F. oxysporum*, *M. phaseolina*, *B. cinerea* and *E. turcicum*. [149]

Flowering tops were hydrodistilled and an EO was obtained and tested against two bacteria and two fungi species. Some of the pure compounds isolated from this EO were also tested against the same microorganisms. In average, EO activity was higher than pure components. Thymol, γ -terpinene and *p*-cymene were the major ingredients of this EO. [150]

Malva sylvestris

Leaves extracts. See detailed description for his reference in *Arum palaestinum*. [31]

Anthocyanin-rich extract (plant part/s, solvent/s and extraction method/s are not indicated) had significant inhibition of *S. aureus*, in a concentration-dependent activity. [151]

Flowers and leaves were separately extracted with *n*-hexane, dichloromethane, and methanol, successively. Both extracts were tested against 6 bacterial and 5 fungal species, showing moderate activities (MIC, inhibition zone), compared with three synthetic antibiotics. [152]

Aerial parts and roots were separately extracted with 70% aqueous ethanol, and both extracts were tested against six bacterial strains. Results showed that aerial parts extract inhibited more bacteria, but roots extract was more potent (MIC). [153]

Leaves ethanolic extract was fractionized with *n*-hexane, ethyl acetate and chloroform. The crude extract and the chloroform fraction were tested against *A. actinomycetemcomitans*, *F. nucleatum*, *P. intermedia* and *P. gingivalis*. Chloroform fraction was more active. [154]

Leaves and flowers of cultivated plants were separately steam-distilled yielding two EOs, that were tested against *P. larvae*, *M. plutonius* and *B. subtilis*. Several fractions of these EOs were also tested, and EOs were in average more active than fractions. Notable differences were detected between the chemical compositions of the EOs. The major components of these EOs are presented in **Figure 22** (flowers, leaves, %): eugenol (10.3,46.7), *E*-phytol (5.7,34.4), tricosane (7.7,0.2), 3-methyltricosane (14.9,0.1), pentacosane (8.2,0.2). [155]

Leaves and roots were separately extracted with 75% aqueous methanol, and these extracts had no activity against *S. aureus*, *P. aeruginosa* and *L. monocytogenesis*. [156]

Flowers 50% aqueous ethanol had moderate activity against *A. actinomycetemcomitans* (MIC = 1.67 mg/mL), compared with two antibiotics (chlorhexidine, doxycycline). [157]

Methanolic leaves extract had moderate activity against four bacterial strains, compared with three synthetic antibiotics. The major components of this extract were determined by GC-MS: tetradecanol, oxirane, octadecatrienoic acid and phytol (see **Discussion**). [158]

Aerial parts were hydrodistilled to produce an EO that was tested against eight bacterial strains, showing high activity (MIC), comparing with chlorhexidine as a reference. The detailed chemical composition of this EO was obtained by GC-MS: hexadecenoic acid, 2-methoxy-4-vinylphenol, pentacosane, heptacosane, linoleic acid and phenanthrene. [159]

Leaves ethanolic extract had no effect against *S. aureus*. [160]

Leaves ethanolic extract had moderate activity against *G. vaginalis* isolated from vaginal secretions, but did not inhibit *Candida* spp. The major components of this extract (>5%) were fatty acids. [161]

Seeds were extracted with acetonitrile/water/formic acid solution, 10:9:1 (volumes), and from the resulting extract, nanofibers were prepared. These nanofibers were active against *P. Aeruginosa*, *E. coli*, *E. faecalis* and *S. aureus*. Major components of the extract are listed but no percentages or concentrations are indicated. Most of them are phenolics. [162]

Leaves 70% aqueous ethanolic extract was prepared and applied against *S. enterica* and *E. coli*, resulting moderate inhibition (MIC). [163]

Aerial parts methanolic extract had strong inhibition (MIC, inhibition zone) and antibiofilm against five bacterial strains, compared with two reference antibiotics. The extract major components were (%): 1-heptacosanol 38.41, 17-Pentatriacontene 19.78 and 6,9,12,15-docosatetraenoic acid, methyl ester 8.08%. [164]

Leaves were successively extracted with *n*-hexane, ethyl acetate, and methanol, and separately with acetone and water. Except ethyl acetate extract, other extracts were tested against *S. aureus*, *E. coli*, *P. aeruginosa*, *S. sonnei* and *P. vulgaris*. Results showed moderate activity compared with three other *Malva* species used in this study. [165]

Aerial parts were extracted with 50% aqueous ethanol, and extract was added to several food to test inhibition of two bacterial and two fungal species, that the foods were infected with. Results showed moderate activities (zone inhibition, MIC, respectively). [166]

Leaves aqueous and ethanolic extracts were prepared and had significant activity against herpes (SuHV-1) and bovine (BoHV-1) viruses. [167]

Leaves were extracted with ethanol and fractionized with *n*-hexane, chloroform and ethyl acetate. The remaining material was considered the aqueous fraction. This fraction had notable activity against HIV-1 BaL virus. [168]

Tea that was prepared from flowers of *M. sylvestris* and parts of other four plants, had very notable activity (such as cough stop after five days) on COVID-19 patients. [169]

Micromeria fruticosa

Leaf and stem extracts. See detailed description for his reference in *Arum palaestinum*. [31]

EO was produced by hydrodistillation (plant part/s not indicated) and had significant activity against *F. oxysporum*, *M. phaseolina*, *B. cinerea* and *E. turcicum*. [149]

Aerial parts were hydrodistilled to produce and EO and leaves were extracted with methanol. Both materials were tested against 14 bacterial and 3 fungi species, resulting moderate activity of the EO and no activity of the extract. Major component of the EO were (%): piperitenone 50.61, pulegone 29.19, isomenthone 3.92 and piperitone 3.12 (**Figure 23**). [170]

Aerial parts were extracted with 70% aqueous ethanol and extract was tested against four bacteria and two fungal species. Compared with two antibiotics, extract had weak to no activity. The major ingredients of this extracts were: chlorogenic acid, hesperetin, naringenin, quercetin and ellagic acid (**Figure 24**). [171]

Aerial parts (from several localities) EO was prepared ultrasound hydrodistillation and was tested against 13 bacterial and fungal species. Comparing with four antibiotics (azithromycin, levofloxacin, doxycycline and cefuroxime), EO had moderate activity. [172]

Pollen was extracted with 70% aqueous ethanol and this extract was applied against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. faecalis*. Compared with extracts of two other plants (*Achillea fragrantissima* and *Phoenix dactylifera*), this extract had significant and higher activity. [173]

Defatted (petroleum ether) leaves and stems were extracted with methanol, and resulting extract was fractionized with water, chloroform and *n*-butanol and *n*-hexane. Extracts were tested against nine bacterial species, and apart from *n*-hexane fraction, all other extracts had moderate activity, compared with reference antibiotics of gentamycin. [174]

Leaves, stems, flowers and roots were separately and successively extracted with *n*-hexane, ethanol and water (12 extracts). Aqueous, ethanolic and *n*-hexane extracts were tested against three bacterial and a fungal species, resulting ethanolic extract as most active and *n*-hexane extract was the weakest. Major components of the combined extracts were: menthone, menthol, pulegone and oleamide (**Figure 25**). [175]

Salvia fruticosa

Leaf and stem extracts. See detailed description for his reference in *Arum palaestinum*. [31]

EO was produced by hydrodistillation (plant part/s not indicated) and had significant activity against *F. oxysporum*, *M. phaseolina*, *B. cinerea* and *E. turcicum*. [149]

Leaves were hydrodistilled and an EO was obtained and tested against two bacteria and two fungi species. Some of the pure compounds isolated from this EO were also tested against the same microorganisms. In average, EO activity was higher than pure components. Eucalyptol, β -caryophyllene and camphor (**Figure 26**) were the major ingredients of this EO. [150]

Flowers aqueous extract was tested against *S. aureus*, *C. albicans*, *E. coli*, *B. subtilis* and *P. Aeruginosa*, and found inactive. [176]

EO of aerial parts was produced by hydrodistillation and tested against 17 bacteria species, resulting very strong activity (MIC). The major ingredients of this EO were (%), **Figure 26**): eucalyptol 15.7, α -thujone 20.1, camphor 12.6, β -caryophyllene 11.8, α -humulene 7.52 and viridiflorol 6.34. [177]

Aerial parts were hydrodistilled affording EO that was tested against 10 bacterial species, resulting high activity (inhibition zone). The chemical composition of this EO similar to the previous report. [178]

Leaves and stems were extracted with 90% aqueous ethanol and extract was tested against four bacterial and fungal species, resulting significant activity. [179]

Aerial parts EO was prepared by hydrodistillation and was tested against eight bacterial and eight fungal species. The test included activity of some natural products isolated from EO. Results (MIC) showed that these compounds were very highly active, and they exceeded the EO. The major constituents of this EO were (%): eucalyptol 49.34, camphor 7.53, β -pinene 7.38, myrcene 7.38 and α -pinene 5.15. [180]

Leaves were extracted with 80% aqueous ethanol and the extract was tested against *S. aureus*. Comparing with two commonly used antibiotics (vancomycin and oxacillin), extract had strong activity (MIC = 0.25-0.5 mg/mL). [181]

EO (plant part/s not indicated) was prepared by hydrodistillation, and tested against *S. aureus*, *S. epidermidis*, *E. faecalis*, *B. cereus*, *E. coli* and *C. albicans*. The EO was tested separately and as 2% of mouthwash formulation, that contained EOs of other plants. Compared with other EOs, it had moderate activity. [182]

Aerial parts were separately extracted with water and ethanol, and both extracts were tested against four bacterial strains, resulting the same high activity (MIC). [183]

Leaves were extracted with 70% aqueous ethanol and extract was fractionized with other solvents, but fractions were not tested for antibacterial activity. The crude extract was tested separately or in combinations with olive and balsam oil, against five bacteria species. Results showed significant activities with moderate synergistic effect. [184]

Aerial parts were hydrodistilled to produce EO that was used to prepare three mouthwash formulations, in various concentrations, with EOs of *Elettaria cardamomum* and *Lavandula angustifolia*. Each one of the three EOs and each one of the formulations was tested against four bacteria species showing weak to moderate inhibition. [185]

Aerial parts from three different location were hydrodistilled to obtain EOs, that were applied against adhesion of *Klebsiella pneumoniae*. Slight differences were found in the activities (significant) or the compositions of these EOs, where the major component was eucalyptol. [186]

Leaves EO was obtained by hydrodistillation and was tested against *K. pneumoniae*, *E. coli*, *S. aureus*, *B. subtilis*, *C. albicans* and *C. parapsilosis*. Compared with the EO of *Salvia aramiensis*, both species showed strong inhibition but *S. fruticosa* had stronger effect. Chemical compositions were almost the same, as shown in figure 26. [187]

Aerial parts EO was produced by steam distillation and tested against seven bacterial strains. The tests were performed separately and in combination with two antibiotics: amikacin and ciprofloxacin. When the EO was tested separately, comparing to the EO of *Salvia ringens*, both materials had almost the same activity, and both were very weak compared to antibiotics. When tested in combination with each one of the antibiotics, clear synergism was detected. The major compounds in this EO were (%): β -thujone 54.2, γ -cadinene 9.2 and β -caryophyllene 5.1 (**Figure 26**). [188]

Seeds EO was prepared by hydrodistillation and fixed oil (FO) was prepared by extraction with *n*-hexane. Both materials were tested against 7 bacteria and 3 fungi species, resulting weak activities. FO contained mainly fatty acids and alkanes, while the major components of EO were (%): palmitic acid 5.27, sclareol oxide 14.5, di-*n*-butylphthalate 9.21, geranyl linalool 9.11 and β -cadinene 16.9 (**Figure 27**). [189]

Aerial parts were separately extracted with cyclohexane (CHX), ethyl acetate (EA), dichloromethane (DCM) and methanol (MeOH). Extracts were applied against seven bacteria species, resulting moderate activity, where CHX extract was most active and EA was least active. A total of 123 compounds were identified in these extracts with six compounds that were isolated for the first time from this plant (**Figure 28**). [190]

Ethanollic extract of aerial parts was prepared and tested against 42 bacterial and fungal species, in two doses: 50 and 200 μ L. Results showed moderate inhibition zones or no activity at all, contrary to many antibiotics that were used as positive control. The major constituents of this extract were (%): camphor 20.27, borneol 9.59, β -caryophyllene 8.11 and lupeol acetate 6.28 (**Figure 29**). [191]

Aerial parts were extracted in two procedures: successively with DCM, EA and methanol; and separately with ethanol and water. The aqueous and ethanolic extracts were tested against 11 bacteria (reference: streptomycin) and 7 fungi species (reference: ketoconazole). Compared with reference, weak activities were recorded. [192]

Leaves EO was produced by hydrodistillation and tested against *M. Furfur*, *T. Rubrum* and *T. beigeli* fungi. Some major ingredients of this EO were tested for the same activity. Results showed that EO had strong activity, slightly more than its single components. Major components of this EO were β -caryophyllene and camphor. [193]

Aerial parts EO was obtained by hydrodistillation and analyzed for its composition. This EO and some of its major components were tested against 5 fungal species showing high potency. The major components were as reported in previous works in this table. [194]

Aerial parts EO (hydrodistillation) and some of its major components were tested against 8 bacterial strains, where components had higher activity. EO and components had notable activity against herpes simplex virus 1. The major ingredients of this EO were as indicated above. [195]

Leaves EOs of three plants (*Coridothymus capitatus*, *Origanum dictamnus* and *Salvia fruticosa*) were produced by hydrodistillation, and applied in several combinations against viral strains that infect respiratory system. Results ranged from none to high activity. [196]

Sinapis alba

Leaves extracts. See detailed description for his reference in *Arum palaestinum*. [31]

Seeds cold press EO was produced and tested against 18 bacteria species and found inactive. Major components of this EO were (%): A, 48.7 and B, 42.08 (**Figure 16**). [115]

Seeds methanolic extract was active against *E. coli*, *S. enteritidis* and *S. aureus*, but authors did not provide numerical values. Two of the major components of this extract, 4-hydroxy-3-nitrophenylacetic and sinapic Acids (**Figure 30**), were also tested and found highly active (MIC). [197]

Seeds were grinded to enable the enzymatic hydrolysis of sinalbin to produce 4-hydroxybenzyl isothiocyanate (4HBITC, **Figure 31**). This compound was extracted with super critical carbon-dioxide and stabilized to obtain an active, commercial antibacterial formulation. It was added to several foods tested and found active against 7 bacteria species that usually infect these foods. [198]

Seeds were extracted with super-critical CO₂ to produce an EO, which was analyzed yielding phenethyl isothiocyanate, C₆H₅CH₂CH₂NCS (PEITC, major ingredient) and some of its derivatives. Compared with tetracycline, the EO and PEITC had strong activity against *P. asaccharolytica*, *P. gingivalis*, *S. mutans* and *S. sobrinus*. The derivatives that had high activity were: benzyl isothiocyanate C₆H₅CH₂NCS and benzoyl isothiocyanate C₆H₅CONCS. [199]

Seeds EO was produced by hydrodistillation and was active against *E. coli*, *K. pneumoniae*, *P. vulgaris* and *S. epidermidis*, but not against *B. cereus*, *E. faecalis* and *S. marcescens*. The major components of this EO were (%): benzyl nitrile C₆H₅CH₂CN 12.05, thymol (figure 20) 7.20, benzyl isothiocyanate C₆H₅CH₂NCS 64.89 and 2-phenyl isothiocyanate C₆H₅CH₂CH₂NCS 6.5. [200]

Commercial roots extract was active against *Xanthomonas perforans*, a pathogen that causes damages to tomato plants (*Solanum lycopersicum*). [201]

Seeds *n*-hexane extract had weak activity against three bacteria species, and significant activity against two fungi species. [202]

Seeds were extracted by steam distillation to obtain an EO, which was tested against nine bacterial strains, in two procedures: EO separately or encapsulated in genipin-strengthened capsules. The second activity was referred to allyl isothiocyanate (AITC), the major component (71.06%) of the EO. The capsules had stronger effect. The other major component was cyclopropyl isothiocyanate (12.16%). [203]

Seeds aqueous extract had no activity (three concentrations) against *B. cereus*, *L. monocytogenes*, *E. coli* and *S. typhimurium*. In this study, it was also reported that *F. vulgare* leaves aqueous extract had no activity in the same procedure. [204]

Fruits were hydrodistilled to afford an EO, and the fruits EO of *Brassica juncea* was obtained and studied, comparatively. Both EOs and oleoresins obtained from the fruits of the two plants, were tested against five fungal and four bacterial species, showing moderate activities. The major component of *S. alba* EO was 1-butene-4-isothiocyanate. [205]

Fresh leaves and fresh seeds were separately extracted (ultrasound-assisted) with aqueous ethanol in several ratios, but only the 80% extract was tested against five bacterial and a fungal species, showing moderate results. As salad preservative, extract had significant activity. [206]

70% Aqueous ethanol was used to prepare an extraction (plant part not indicated), and it was tested against *C. albicans*, showing moderate activity. [207]

Roots, stems, leaves and flowers, were separately and successively extracted with petroleum ether, ethanol and DCM. All (12) extracts were tested against *E. coli*, *S. aureus* and *P. aeruginosa*, showing either weak or no activity. [208]

Leaves were separately extracted with *n*-hexane, ethanol and water, and the three extracts were applied against *E. Coli*, *S. aureus* and *C. albicans*. Results showed moderate to high activity, where ethanolic extract was most active. [209]

Commercial EO containing 12% 4HBITC was tested separately or in combination with thymol or carvacrol, against *Salmonella* ssp. Results revealed moderate activity of the EO alone, and moderate synergistic when applied in combination with thymol or carvacrol. Results were dose dependent. [210]

Seeds were extracted with *n*-hexane and ethanol, and each extract was tested against *B. subtilis*, *P. aeruginosa* and *C. albicans*, in three different concentrations. Compared with controls (ciprofloxacin, fluconazole and erythromycin), results ranged from no to moderate activity. [211]

Commercial EO was tested separately and in combination with carvacrol against *Salmonella* ssp. in refrigerated, ground chicken meat, in variety of concentrations of each material. Moderate effect was detected. [212]

Leaves, flowers and fruits were separately extracted with chloroform and 70% aqueous methanol, but only the methanolic extract was tested against *S. aureus*, *E. coli* and *P. aeruginosa*. Activity ranged from no to weak activity, compared to three references. [213]

Seeds aqueous extract was used to prepare a hydrogel that was tested against *S. aureus*, *C. albicans*, *E. faecalis* and *S. mutants*, resulting moderate activities. [214]

Seed powder solution (10%) in DMSO was tested against HSV-1 and HAV-7 viruses, resulting low (23%) to moderate (54.3%), virucidal effect, respectively. [215]

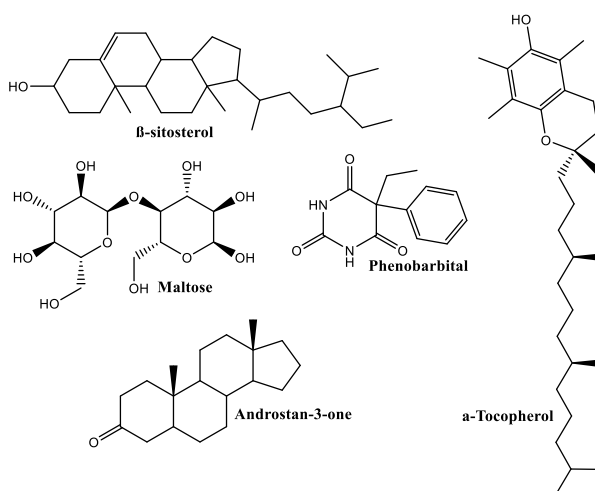


Figure 3: Antiviral agents from *A. palaestinum* [36]

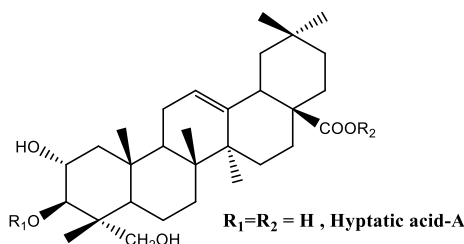


Figure 4: General structure of saponins isolated from *C. persicum* tuber [44]

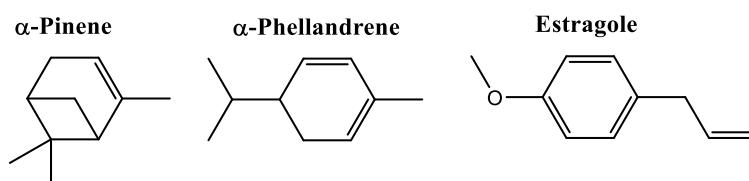


Figure 5: Major components of aerial parts EO of *F. vulgare* [45]

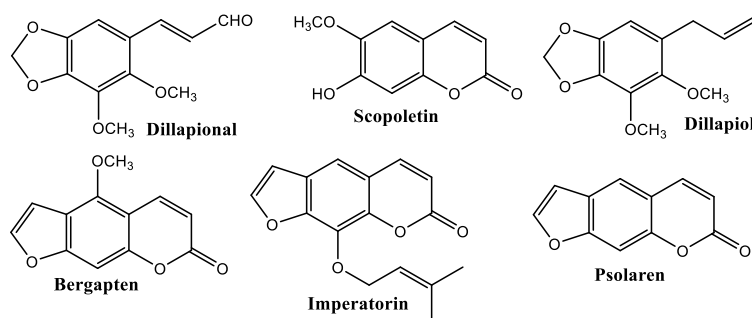


Figure 6: Antibacterial NPs from the stem methanolic extract of *F. vulgare* [46]

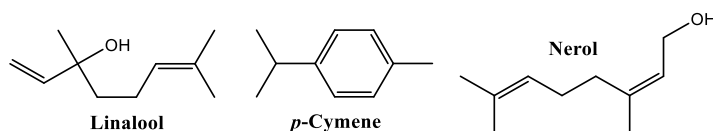


Figure 7: Major components of fruits EO of *F. vulgare* [47]

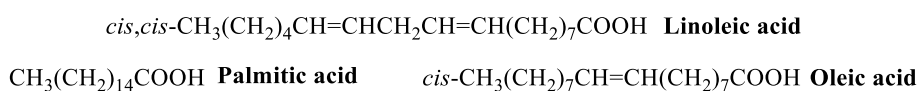


Figure 8: Fatty acids from methanolic and ethanolic extracts of *F. vulgare* [50]

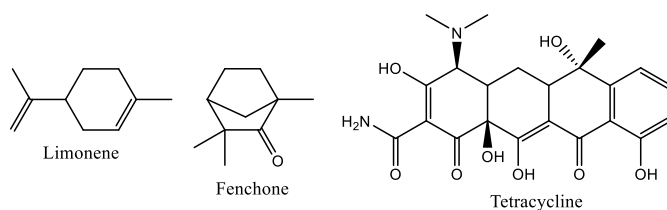


Figure 9: Major components of seeds EO of *F. vulgare* and tetracycline [53]

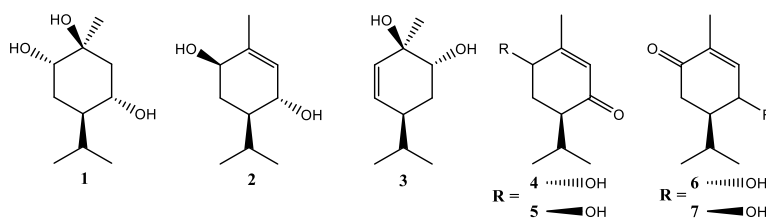


Figure 10: NPs isolated for the first time from DCM-Methanol extract of *F. vulgare* [57]

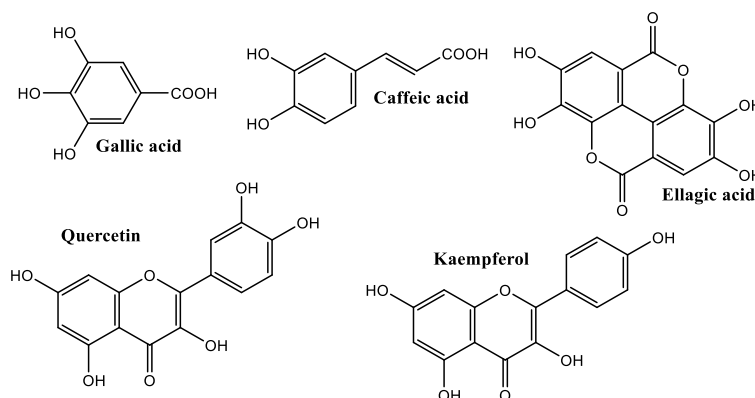
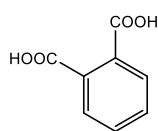
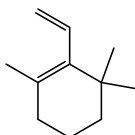


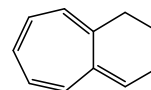
Figure 11: Major phenolics from the 80% aqueous methanolic extract of *F. vulgare* [62]



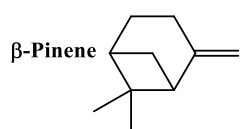
o-Benzenedicarboxylic acid



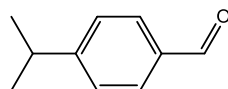
1,3,3-Trimethyl-2-vinyl-1-cyclohexene



1H-Benzocycloheptene

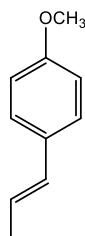
Figure 12: Major components of EO of *F. vulgare* [67]


β-Pinene

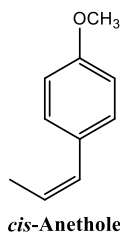


Cuminal

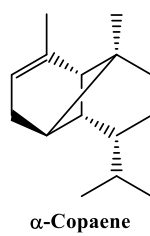
p-Cymene (Figure 7)

Figure 13: Major components of leaves EO of *F. vulgare* [94]


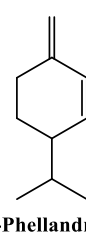
trans-Anethole



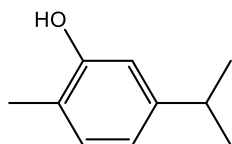
cis-Anethole



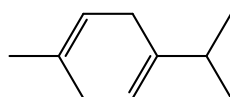
α-Copaene



β-Phellandrene

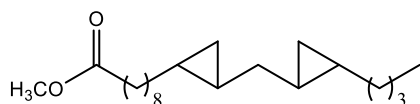
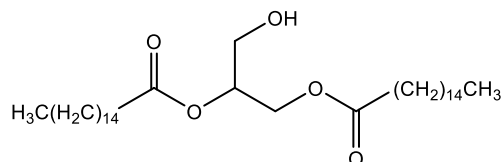
Figure 14: Major components of fresh leaves EO of *F. vulgare* [104]


Carvacrol



γ-Terpinene

p-Cymene (Figure 7)

Figure 15: Major components of leaves EO of *M. syriaca* [113]

A, Cyclopropanenonanoic acid, 2-[(2-butylcyclopropyl) methyl]-, methyl ester

B, Hexadecanoic acid, 1-(hydroxymethyl)-1,2- ethanediyl ester
Figure 16: Major components of leaves cold press EO of *S. alba* [115]

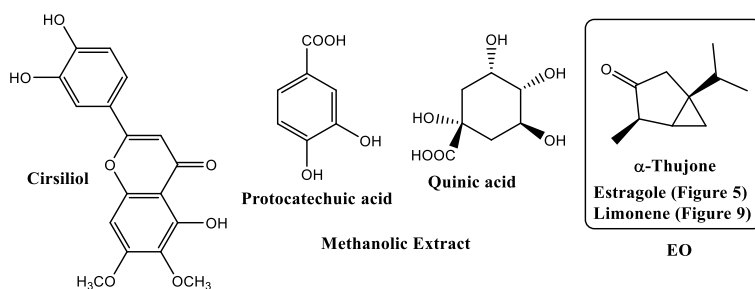


Figure 17: Major components of seeds EO and methanolic extract of *F. vulgare* [118]

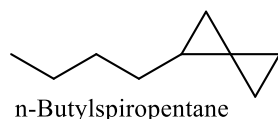


Figure 18: n-Butylspiropentane from methanolic extract of *G. tournefortii* [125]

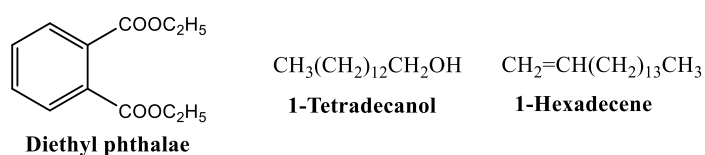


Figure 19: Major compounds in seeds aqueous extract of *G. tournefortii* [130]

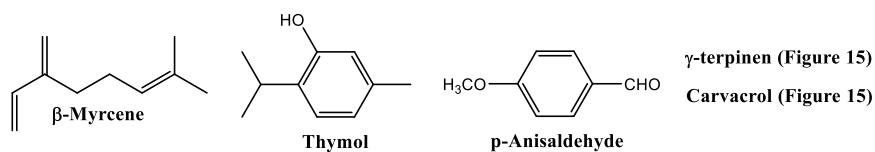


Figure 20: Major components of leaves and stems EO of *M. syriaca* [141]

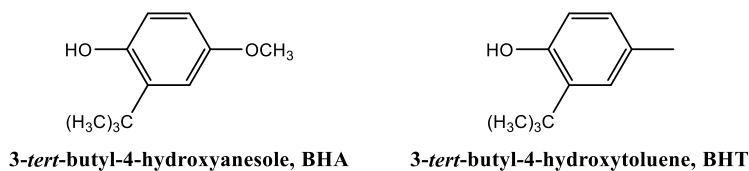


Figure 21: Synthetic antibacterial agents used as control for activity *M. syriaca* EO [146]

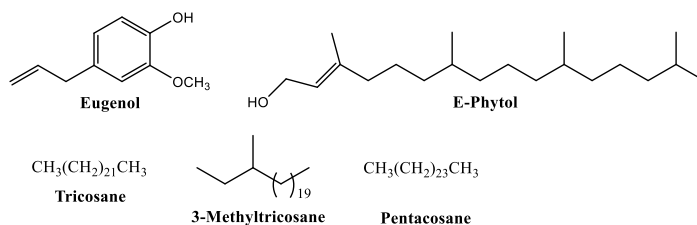


Figure 22: Major compounds in flowers and leaves of *M. sylvestris* EOs [155]

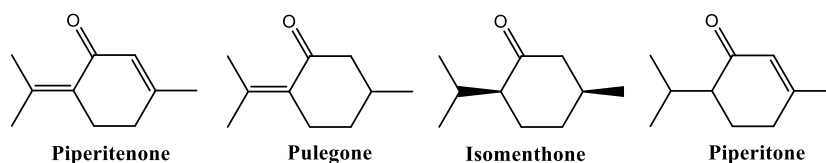


Figure 23: Major components of leaves EO of *M. fruticosa* [170]

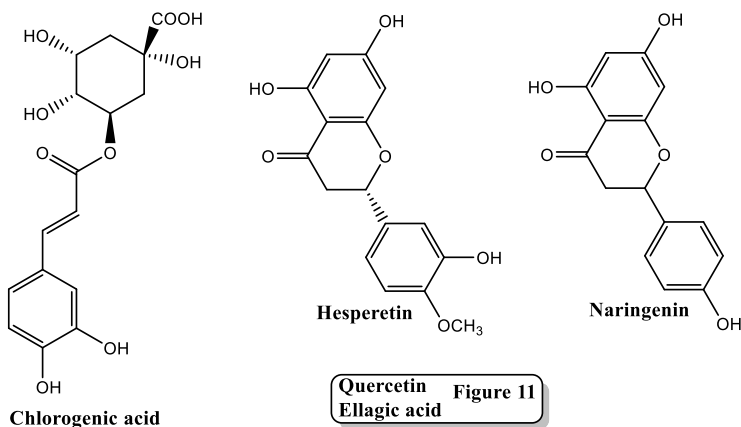


Figure 24: Major phenolics of aerial parts 70% aqueous ethanol extract of *M. fruticosa* [171]

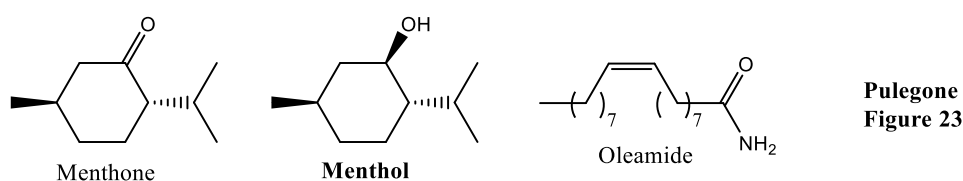


Figure 25: Major compounds in combined (parts and solvents) extracts of *M. fruticosa* [175]

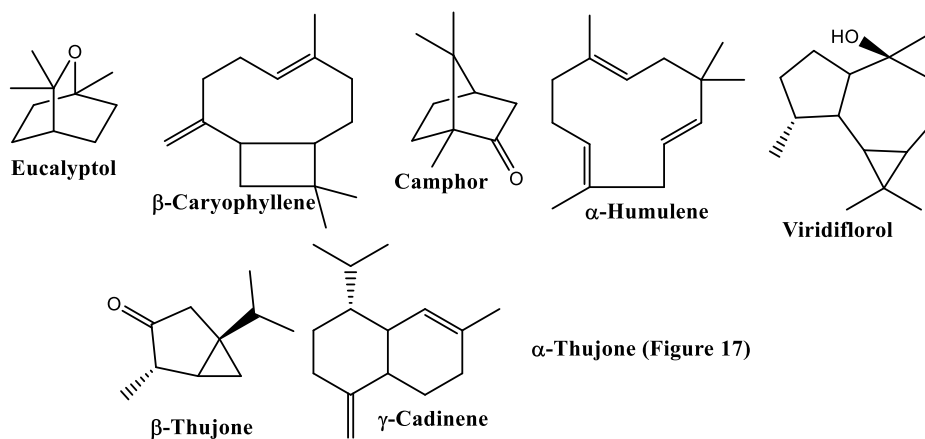


Figure 26: Major ingredients of *S. fruticosa* aerial parts EO [150,177,188]

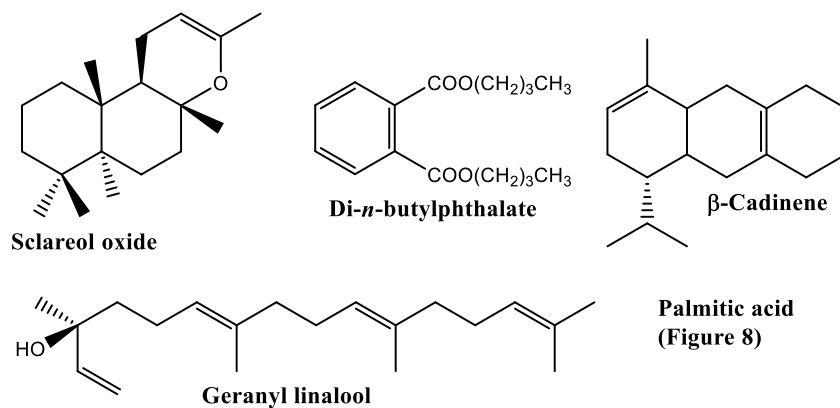


Figure 27: Major components of *S. fruticosa* seeds EO [189]

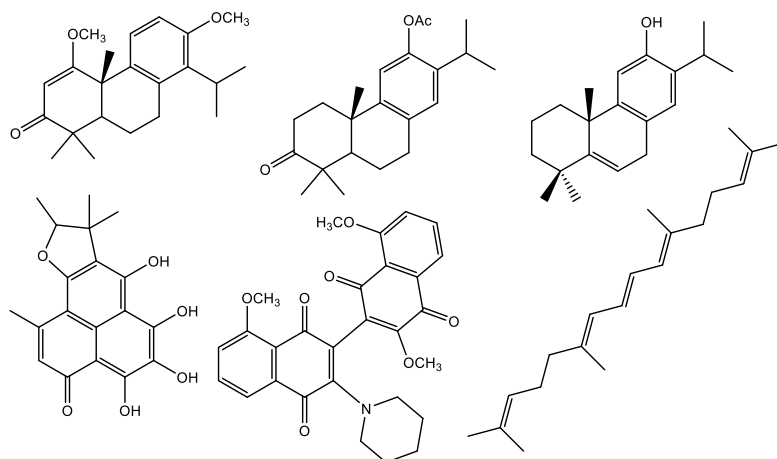


Figure 28: Components isolated for the first time from *S. fruticosa* aerial parts extracts [190]

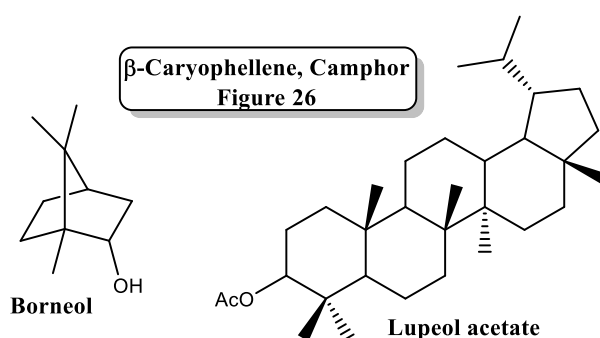


Figure 29: Major ingredients of *S. fruticosa* aerial parts ethanolic extract [191]

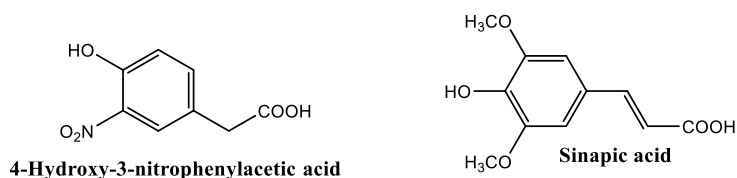


Figure 30: Antibacterial compounds from *S. alba* seeds methanolic extract [197]

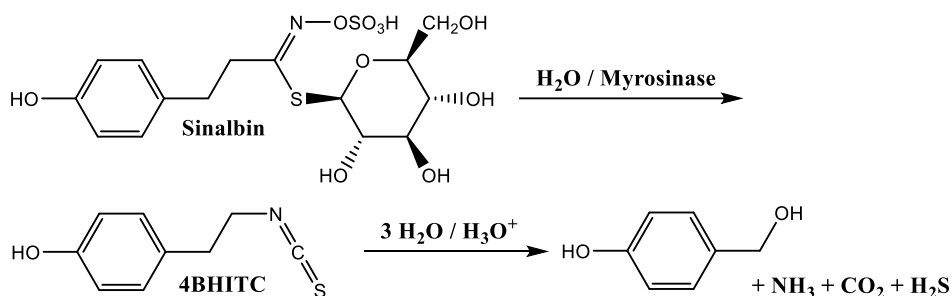


Figure 31: 4-Hydroxybenzyl isothiocyante (4BHITC) production from enzymatic hydrolysis of sinalbin in *S. alba* seeds EO and its acidic decomposition [198]

DISCUSSION

The eruptions of microbial and viral diseases were and still are serious threats to human health along history, and the latest outburst of COVID-19 is an excellent and recent example. There is almost a consensus among researchers and health authorities that humanity on one side, and harmful

microorganisms and viruses on the other side, are in life-or-death combat and race [216]. Antimicrobial resistance to drugs is the major cause of this threat, but drugs (mainly antibiotics) overuse is another important reason [217]. This excessive use is considered by many scholars as one of the major causes of antibiotics resistance [218]. Another important reason of antibiotics resistance is the disposal of untreated antibiotics, like all untreated drugs, to the environment [219].

Disposal of untreated antibiotics, among other drugs, to the environment is becoming an increasing issue of concern due to its adverse consequences [220]. Environmental pollution resulting from untreated antibiotics and their degradation products, has an effect on almost all parts of the environment, especially life forms [221]. In this context, it is important to mention that some of these antibiotics (such as fluoroquinolones: ciprofloxacin and norfloxacin. **Figure 32**) are relatively stable and degrade slowly.

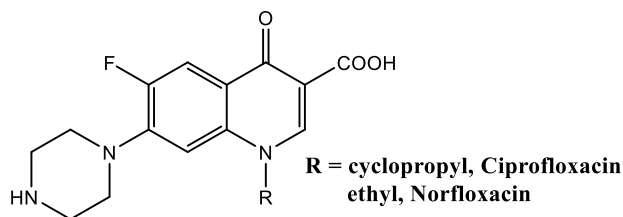


Figure 32: Stable, slowly degradable fluoroquinolone antibiotics [221]

Once this pollution caused, the efforts and methods to remove antibiotics from the environment are enormous and costly. For example, A. Huang and colleagues listed more than a dozen methods, chemical, biological and mechanical [222]. M. Segaseta de Ilurdoz and colleagues focused on removal of antibiotics contaminations from aquatic environments, and they presented some efficient but expensive methods, such as use of H₂O₂ or O₃ in combination with UV-radiation [223]. And in a recent example, H. Shi and colleagues published their results of treating antibiotics pollutions with composite material Ag/PW₁₂/TiO₂ and UV radiation, and proposed possible mechanism of degradation [224]. All these considerations lead to the vital need of developing plant-based antimicrobial and antiviral drugs.

Arum palaestinum was not frequently published for antimicrobial or antiviral activity, as we saw in **Table 1** [31-36]. L. Abu-Qatouseh and his colleagues have tested the polyphenolic extracts of 8 plants and reported that *A. palaestinum* had the lowest content [225]. They tested these extracts against *Propionibacterium acnes* and found it most active (lowest MIC and highest inhibition zone). According to this report, *Malva sylvestris* had medium phenolics content and very low antibacterial activity. These results raise a few concerns. First, it is reported in the same publication that *Eucalyptus globulus* (leaves) had the highest total phenolic content and the highest antibacterial activity. Second, this result is consistent with the very well-known role of flavonoids as active antibacterial agents [226]. Third, the report of L. Abu-Qatouseh and his colleagues contradicts the finding K.A. Shadid and his colleagues [165], in total phenolic content of leaves methanolic extract of *M. sylvestris* (166 and 21 mg GAE/g extract, respectively); and in antibacterial activity (very low vs. significant), keeping in mind that tests were done against different bacterial species. Fourth, the phenolic content of *E. globulus* leaves methanolic (80%) extract is 21 mg GAE/g extract, while S. Dezsi and his colleagues reported 238 mg GAE/g extract [227], and V. Pereira and her colleagues reported 63 mg GAE/g extract [228].

The number of publications of antimicrobial and antiviral activities of *Cichorium pumilum* is also relatively low in **Table 1**: seven [31,37-42]. Interestingly, leaves of this plant are naturally good habitat for microbial biofilm growing, which enables culturing and isolation of microorganisms [229,230]. As for antimicrobial activity.

The use of nanoparticles as antimicrobial agents is widespread [231], and we have cited studies in **Table 1**: *F. vulgare* EO in combination with AgNPs [106] and *M. sylvestris* extracts nanofibers [162]. But the vast majority of antimicrobial nanoparticles reviewed by D. Susanti and her colleagues [231], are produced using plant extracts, mostly as reducing agents, and the final nanoparticles do not contain plant materials. The D-P were used for these preparations, and a summary of selected reports are presented in **Table 2**.

Table 2: Antimicrobial Nanoparticles Prepared Using D-P-derived materials

| Plant/Material | Nanoparticle | Microorganisms/Reference |
|--|--------------------------------|--|
| <i>C. pumilum</i> , leaves aqueous extract | Ag | <i>A. aflatoxiformans</i> , <i>A. ochraceus</i> [232] |
| <i>F. vulgare</i> , seeds aqueous extract | Ag | <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> [233] |
| <i>F. vulgare</i> , seeds aqueous extract | ZnO | <i>S. aureus</i> , <i>E. coli</i> , <i>Y. enterocolitica</i> , <i>B. cereus</i> [234] |
| <i>G. tournefortii</i> , aerial parts aqueous extract | Ag | <i>S. aureus</i> , <i>B. cereus</i> , <i>S. typhimurium</i> , <i>E. coli</i> [235] |
| <i>G. tournefortii</i> , fresh leaves aqueous extract | Ag | <i>S. aureus</i> , <i>E. coli</i> , <i>C. albicans</i> [236] |
| <i>G. tournefortii</i> , fresh leaves aqueous extract (GT) | Ag@GT AgNPs contain GT | <i>C. krusei</i> , <i>C. guilliermondii</i> , <i>C. glabrata</i> , <i>C. albicans</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. typhimurium</i> , <i>E. coli</i> , <i>S. pneumoniae</i> , <i>B. subtilis</i> [237] |
| <i>G. tournefortii</i> , fresh leaves aqueous extract (GT) | Au@GT AuNPs contain GT | <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. krusei</i> , <i>C. guilliermondii</i> , <i>P. aeruginosa</i> , <i>E. coli</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>S. typhimurium</i> , <i>S. pneumonia</i> [238] |
| <i>G. tournefortii</i> , fresh leaves aqueous extract | Au | <i>S. aureus</i> , <i>E. coli</i> , <i>B. subtilis</i> , <i>C. albicans</i> [239] |
| <i>M. sylvestris</i> , flowers aqueous extract | Ag | <i>E. coli</i> , <i>S. aureus</i> , <i>S. typhimurium</i> , <i>B. subtilis</i> [240] |
| <i>M. sylvestris</i> , flowers aqueous extract | Ag | <i>E. coli</i> , <i>S. aureus</i> [241] |
| <i>M. sylvestris</i> , unknown part/s aqueous extract | Fe ₃ O ₄ | <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>Corynebacterium</i> [242] |

One of the most noticeable findings that emerges from carefully reading the data in **Table 1**, are the differences between results that were reported about the same plant. For example, comparing the chemical compositions of aerial parts EOs of *F. vulgare*, obtained by the same method of hydrodistillation and from the same plant parts (aerial), shows notable differences between the reports of G. Ruberto and his colleagues [45] vs. M. Araque and her colleagues [49] and M.G. Miguel and her colleagues [54]. In the first report, *trans*-anethole (**Figure 14**) is a minor component while in two other studies it's a major component.

It is important to mention that the study of M.G. Miguel and her colleagues [54] has an additional value: it presents the chemical compositions of *F. vulgare* EOs depending on several variables: time of extraction, plant part, locality (9 different countries), and most important, method of extraction (steam distillation, hydrodistillation, *n*-pentane extraction and *n*-hexane extraction).

Such differences can be understood even when very close extracting solvents are used, as in the cases of M. Gulfranz and colleagues [50], compared with S. Soylu and colleagues [53]. These groups used the same parts of *F. vulgare*, but different extractors: methanol and ethanol, respectively, resulting notable differences in activities and chemical compositions.

Another inconsistency of chemical compositions can be found in the report of R.K. Upadhyay [67], compared with many other reports such as W-R. Diao and his colleagues [64]. The major constituents found by R.K. Upadhyay were 9-octadecenoic acid, *o*-benzenedicarboxylic acid, 1,3,3-trimethyl-2-vinyl-1-cyclohexene, 1H-benzocycloheptene; while many other groups found mainly oxygenated monoterpenes such as *trans*-anethole and estragole. Needless to say, that in all these studies same plant part (seeds) was used and same method of production (hydrodistillation).

The work of B. Ayoubi and P. Baradari [126], is an example of inaccurate and very misleading scientific reporting. Authors use the common name of coriander for *Gundelia tournefortii*, which is completely wrong. The common name of coriander belongs to the plant *Coriandrum sativum*, and the common name of *G. tournefortii*, which is tumble thistle. *C. sativum* is a member of the Apiaceae family while *G. tournefortii*, is belongs to the Asteraceae family. And more important, as far as our extensive literature search could reach, we found no scientific report of the presented compounds by B. Ayoubi and P. Baradari,

especially *E*-2-dodecenal or (*2E*)-dodecanal, in *G. tournefortii*. Authors cite I. Kobo and his colleagues [243] for the presence of this and other aldehydes in the “fresh leaves of *Gundelia genius*”. But reading the report of I. Kobo *et al.* reveals the fact that they clearly indicate that coriander is *C. sativum*, and it contains *E*-2-dodecenal.

A.N. El Gendy and his colleagues studied the chemical composition and antimicrobial activity of essential oil of wild and cultivated *O. syriacum* plants grown in Sinai, Egypt [139]. Their findings are quite interesting, and considering the cultivation environment of the plants in the Sinai desert, some of the inconsistencies in **Table 1** can be understood. This means, that the EO or the plant extract is the final product, and its composition and activity depend on many variables. Methods of extraction, solvents, temperature etc., are easily controlled variables. But climate, soil, irrigation and rain, locality, seasonality, ripening stage, cultivation and farming methods (if not wild); are also very important factors.

A.S. Abdelbaky and his colleagues from Egypt as well (like A.N. El Gendy and his colleagues), found clear influence of fertilizers use and types on the yield, chemical composition and activities of EO of *F. vulgare* [244]. M. Abdellaoui and his colleagues found clear differences between the chemical compositions of cultivated and wild EOs of *F. vulgare* (%): estragole 60.01 and *E*-anethole 22.15 in the cultivated plants, while 35.33 and 52.27 in the wild plants [245]. S. Zein and her colleagues from Lebanon tested, among many variables, the fatty acids composition of EOs of *M. syriaca*, wild and cultivated, before and after flowering, and found significant differences [246]. For example, palmitic acid (*n*-C₁₅H₃₁COOH) is 14.2% of the EO of wild plants before flowering and 15.12% in cultivated plants, and 5.18% and 3.31%, after flowering, respectively. S. Abu-Lafi and his colleagues from Palestine and Israel found notable differences in the concentrations of terpenoid compounds in the EOs of *M. syriaca* harvested in nine different locations [247]. For example, the concentrations of *p*-cymene were (%): 15.20, 15.83, 17.24, 18.40, 18.98, 19.13, 24.37, 23.87, 26.53. A year earlier, the same research group investigated the seasonality influence on the leaves EO of *M. syriaca* variables: yield and the ratio of thymol to carvacrol concentrations [248]. When EO was produced by steam distillation, the ratio of thymol:carvacrol in February 2004 in a certain location was 1:1.78, while in May it was 1:5.29. C. Dincer and his colleagues from Turkey investigated the phenolic content of 80% aqueous methanolic extract of leaves, as well as yield of EOs, for cultivated and wild plants of *S. fruticososa* [249]. They reported that for wild plants, the total phenolic content was 42.25 mg of gallic acid equivalent (GAE) per 1 g of dry plant matter, and the EO content was 1.82 mL. For cultivated plants the values were 45.21 and 1.48, respectively. In addition, if the dry leaves powder is properly stored, the reported values did not significantly change, but the antioxidant activities were clearly different.

Likewise, storage of dry or fresh plant matter or its products that is a handling variable, the drying process has also clear influence on these products and their activities. M.H. Alqarni and his colleagues from Saudi Arabia and Egypt found notable effect of the drying conditions of aerial parts of *M. fruticososa* on the yield, composition and antimicrobial activity of the EO that was obtained from these parts [250]. Tests were done for fresh parts, freeze-dried and shade-dried, and the results are presenter in **Table 3**.

Table 3: EO Content, Major Components and Antimicrobial Activity of Aerial Parts of *M. fruticososa* Subjected to Different Drying Conditions [250]

| Plant Matter | EO content ^a | Two Major components ^a | MIC (µg/mL) ^b |
|--------------|-------------------------|--|--------------------------|
| Fresh | 0.28 | pulegone 23.70, <i>l</i> -menthone 19.54 | 14.35 |
| Freeze-dried | 0.27 | pulegone 22.14, <i>l</i> -menthone 17.47 | 14.35 |
| Shade-dried | 0.07 | <i>l</i> -menthone 20.40, pulegone 13.79 | 14.35 |

a) % b) Average against: *E. coli*, *P. Aeruginosa*, *S. aureus*, *B. cereus* and *C. Albicans*

It is important to mention that even though the average MIC values are identical, and the individual value for each microorganism is also identical (12.5, 9.125, 18.25, 18.25 and 9.125, respectively), authors concluded that “oil samples showed stronger activity against *P. aeruginosa* and *C. albicans*”.

The last example of the influence of handling plant matter conditions was demonstrated by M. Yousefi and colleagues from Iran [251]. They found out that the heating method (steam, hot air, hot water), temperature, heating duration and cooling (“deheating”) duration; all these have significant effects on myrosinase content and antibacterial (*B. subtilis*, *B. coagulans*, *S. cerevisiae* and *Z. rouxi*) activity of *S. alba* seed powder.

The use of *S. alba* seed powder as food preservative was already mentioned in **Table 1**: the work of J.J. Li and colleagues [198]. A. Hosseinvand and A. Sorkhinejad used this powder as ground beef preservative since it had protection activity against *S. aureus* and *E. coli* [252]. J.J. Li and colleagues as well as several other studies, link the antibacterial activity with 4HBITC that is produced in the enzymatic hydrolysis of sinalbin [198, **Figure 31**]. B.G. Shofran and colleagues link this activity to sinigrin and its hydrolysis products, that are shown in **Figure 33** [253]. It is important to indicate that the concentration of sinigrin is much higher than the concentration of sinalbin in seeds of *S. alba* [254].

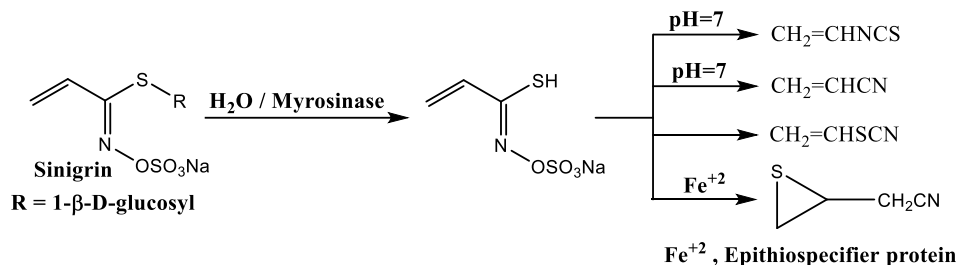


Figure 33: Enzymatic hydrolysis of sinigrin in *S. alba* seeds powder and its decomposition under different biological conditions [253]

To conclude the discussion about *S. alba*, we will add two important reports. First, U. Timmerer and her colleagues found out that antibiotics such as enrofloxacin have toxic effect on the germination of *S. alba* roots [255]. This result emphasizes the importance of preventing disposal of antibiotics to the environment. Second, in recent years there were some concerns about possible toxicity of *S. alba* seeds and its food product, mustard, to humans and animals. These concerns were issued mainly due to the presence of bisphenols (**Figure 34**) in the seeds and in mustard [256,257].

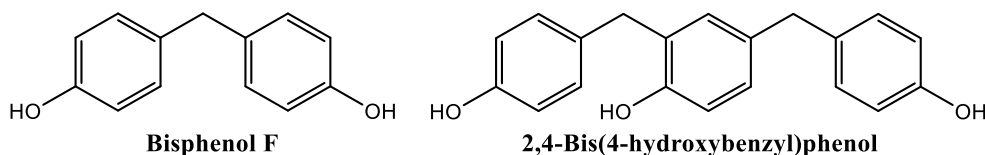


Figure 34: Bisphenols in *S. alba* seeds [257]

But recent toxicology studies showed that these compounds are present in safe amounts in average mustard consumption, and *in vivo* (mice) studies revealed no toxic effects of seeds consumption [258].

The mentioned above results bring our discussion, once more, to the importance of accuracy in scientific reporting. For example, the chemical composition of the methanolic extract of *M. sylvestris* leaves reported by S. Doweck and her colleagues [158], is quite confusing. In the results section of this paper, under the title of “GC-MS analysis”, authors reported that the major volatile components of the extract are tetradecanol, oxirane, octadecatrienoic acid and phytol. No concentrations or percentages were indicated, but authors direct readers to figure 1, where they presented a chromatogram. Interestingly, these compounds are not listed in table 3 (in the article), where authors presented the “major compounds” in the extract. In addition, it is not obvious to detect oxirane (ethylene oxide) with such high concentration in any plant extract. As for tetradecanol, the stereochemistry of the double bond and the position of the hydroxyl group are not indicated, and this means that the detected compound can be one of many isomers. The same considerations can be applied to the reported octadecatrienoic acid, which in summary, makes this chemical composition report partially useful.

The last part of this discussion will focus on pure or single antibacterial compounds, and we will take D-limonene as representing example. The majority of drugs that were developed from plants, started by using an extract or EO, then identifying the active molecule/s (“hit”) and then using it or prepare some more active chemical modifications. Limonene was mentioned in **Table 1** as one of the major components of *F. vulgare* [52,53,72,73,92,93,99,103,118] and shown in **Figure 9**.

Among several reports of the antimicrobial activities of limonene, it was reported to have strong activity against the fungus *Candida parapsilosis*, an aggressive and strong inflammation-inducer fungi is

usually treated with fluconazole (**Figure 35**) [259]. D-Limonene is also powerful antibacterial against *Listeria monocytogenes*, one of the worst (deadly) and most contaminating food pathogens, which is usually treated with (among other drugs) gentamicin (**Figure 35**) [260].

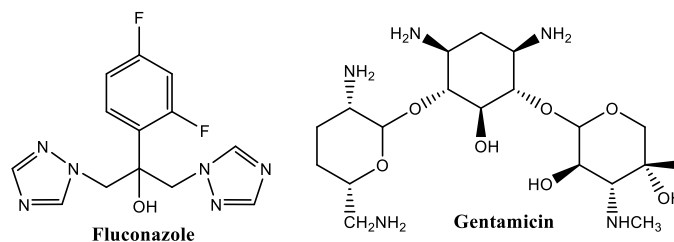


Figure 35: Fluconazole antifungal and gentamicin antibacterial agents [259,260]

Fluconazole has some adverse side effects, especially for pregnant women and when co-administered with other drugs [261]. And according to the review article of P. Escribano and J. Guinea, *Candida parapsilosis* is “a new emerging threat in the fungi arena”, has developed resistance to fluconazole [262]. Gentamicin also showed some negative side effect, where one of the worst is acute kidney injury, according to epidemiological study of N.M. Selby and his colleagues [263]. And according to the published results of R.M. Hanes and Z. Huang, the gentamicin-resistance of *Listeria monocytogenes* was significantly increased between 2010 and 2021 [264]. All this data highlights the need for development of antimicrobial and antiviral new agents from natural products like D-limonene.

Selected Wild Edible Non-Deca-Plants with Antimicrobial and Antiviral activity

Many wild plants of Eastern Mediterranean region possess antimicrobial or antiviral activities. Most of these plants are inedible and even toxic, like antimicrobial *Taraxacum officinale* [265], and antiviral *Solanum nigrum* [266]. And among wild, edible non-D-P, there are also many plants that have these properties. In **Table 4** we present five, randomly selected plants.

Table 4: Published Antimicrobial Activities of the Non-D-P in Eastern Mediterranean region.

| Testing Method, Results and Reference/s |
|---|
| <p><i>Allium ampeloprasum</i> Roots and stems were extracted with several solvents, but only aqueous extract was tested against <i>S. aureus</i> and <i>P. aeruginosa</i>. Compared with three commonly used antibiotics, this extract had moderate activity. [267]</p> |
| <p><i>Capparis spinosa</i> Leaves were extracted with chloroform, acetone, water and methanol. Aqueous and methanolic extracts were tested against four bacterial strains, and the activities (MIC) were compared with two antibiotics, showing moderate results. [268]</p> |
| <p><i>Matricaria aurea</i> Flowers were separately extracted with chloroform, ethyl acetate, acetone, ethanol and methanol, and all extracts were tested against 7 bacteria and 6 fungi species. All extracts were active but ethanolic and methanolic extracts were most potent. [269]</p> |
| <p><i>Portulaca oleracea</i> Leaves and stems were defatted with petroleum ether and extracted with 95% aqueous ethanol, ultrasonic-assisted, affording organic acids-rich extract. This extract was tested against <i>S. aureus</i>, <i>in vitro</i> and <i>in vivo</i>, in rat model contaminated wounds. Strong inhibition activity was recorded in both tests. [270]</p> |
| <p><i>Scolymus maculatus</i> Whole plant was separately extracted with water, methanol, ethanol, ethyl acetate, and <i>n</i>-hexane, and all extracts were tested against <i>S. aureus</i>, <i>S. typhimurium</i>, and <i>C. albicans</i>. Compared with three commonly used antibiotics, extract had moderate activities, where ethanol and ethyl acetate had strongest inhibitions (MIC). [271]</p> |

CONCLUSIONS

- Some of the Deca-Plants have excellent antimicrobial activity. Others need to be more studied.
- It is important to investigate the roles of single compounds contained in the D-P plants relating to antimicrobial activity.
- As for antimicrobial activity, the superiority of essential oils over extracts is clear.
- There is a significant need for more research of the antiviral potential of the D-P.
- Accuracy and consistency of scientific reporting are vital.

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