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Comparative Secondary Metabolite Analysis and Antimicrobial Assessment of *Agastache foeniculum* (Pursh) Kuntze Leaf and Flower Extracts

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Abstract

Agastache foeniculum (Pursh) Kuntze, a member of the *Lamiaceae* family, is a phytochemically rich yet underexplored species with potential biomedical applications. This study aimed to provide an organ-specific chemical characterization of its secondary metabolites and to evaluate the antimicrobial potential of ethanolic extracts derived separately from its leaves and flowers. Using UHPLC-MS/MS, we identified a total of 54 compounds, including phenolic acids and flavonoids. In total, 35 compounds in the flower extract and 38 in the leaf extract were reported here for the first time. The antimicrobial activity of both extracts was tested against six multidrug-resistant (MDR) clinical bacterial isolates (*Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Citrobacter freundii*, *Achromobacter xylosoxidans*, and *Acinetobacter baumannii*) using seven concentration levels (12.5–87.5%). While the leaf extract showed limited antibacterial effects, the flower extract demonstrated stronger, concentration-dependent inhibitory effects. At concentrations of 62.5% and above, it markedly reduced viable bacterial counts in all tested MDR strains. These findings highlight the importance of organ-specific phytochemical analysis in medicinal plants and suggest that *A. foeniculum*, particularly its flowers, may serve as a promising source of bioactive compounds for further antimicrobial research and development.

Keywords: *Agastache foeniculum*; UHPLC-MS/MS; secondary metabolites; antimicrobial activity; multidrug-resistant bacteria

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1. Introduction

The *Lamiaceae* family comprises over 245 genera and more than 7800 species, many of which are well known for their medicinal and culinary uses. Members of this family are typically aromatic shrubs or herbs, characterized by the production of secondary

metabolites such as essential oils, flavonoids, and phenolic compounds [1]. Prominent genera include *Mentha*, *Thymus*, *Origanum*, *Salvia*, *Melissa* and *Lavandula*, widely employed in traditional medicine and gastronomy [2–7].

Within this family, the genus *Agastache*, commonly referred to as "giant hyssop", comprises approximately 22 species, primarily native to North America. Several species, including *Agastache foeniculum* (Pursh) Kuntze, have been used in ethnomedicine for treating pain, hypertension, and gastrointestinal conditions [8,9]. *A. foeniculum*, in particular, was valued by Indigenous North American peoples for its cardiovascular, respiratory, and digestive applications, and its leaves were also used as a culinary spice due to their characteristic anise-like flavor [10]. Recent studies further demonstrated its therapeutic potential in dermatology: Abbasi et al. [11] reported that the topical application of *A. foeniculum* essential oil significantly accelerated wound healing in mice by enhancing tissue regeneration and reducing oxidative stress.

Phytochemical investigations have revealed a broad array of bioactive compounds in *A. foeniculum* and other *Agastache* species, including methyl chavicol (estragole), phenolic acids, and flavonoid glycosides, which may contribute to its antibacterial, antifungal, antioxidant, anti-inflammatory, and even anticancer properties [12–19].

Recent chromatographic and spectrophotometric studies have reported high levels of rosmarinic acid, chlorogenic acid, caffeic acid, apigenin, apigenin-7-O-glucoside, rutin, and quercetin in *A. foeniculum*, with rosmarinic acid often being the dominant compound [20]. According to Lebedeva et al. [21], the leaves and inflorescences are the primary accumulators of the content of flavonols, catechins, tannins, protopectins, saponins, and carotenoids, with the mass flowering stage being the optimal harvesting time due to peak antioxidant capacity. Similarly, Duda et al. [22] recommended collection during early flowering and afternoon hours to maximize polyphenol yield. Phenological evaluations using the BBCH scale by Vârban et al. [23] have further defined the agronomic stages of several *Agastache* species, supporting optimal harvesting strategies based on developmental phase.

The essential oil (EO) composition of *A. foeniculum* has been extensively studied. Mazza and Kiehn [24] identified 50 components in the EO, with methyl chavicol (estragole) accounting for up to 98%, alongside camphene, *p*-cymene, β-pinene, and α-guaiene. These findings have since been expanded by Nechita et al. [8], who reported 42 volatile compounds using GC–MS, including additional constituents such as eucalyptol, menthone, and caryophyllene. Their study further emphasized the antimicrobial and cytotoxic potential of *A. foeniculum* EO. Similarly, Bălănescu et al. [15] identified 41 EO constituents in the leaves and 36 in the flowers, reinforcing the organ-specific diversity of volatile compounds in the species. Omidbaigi et al. [25] demonstrated that nitrogen fertilization influences EO composition by modulating the relative abundance of major terpenoids. Post-harvest conditions also affect oil content: Mahmoodi Sourestani et al. [26] showed that drying at room temperature resulted in the highest EO yield, while oven drying at 40 °C significantly reduced the oil content.

Although *A. foeniculum* has been widely studied for its essential oil composition, relatively few publications have assessed its antimicrobial activity against clinically relevant human pathogens. Among the available data, the essential oil has shown inhibitory effects against Gram-positive bacteria such as *Staphylococcus aureus* and *Listeria monocytogenes* [27–29]. Antifungal activity has also been demonstrated against *Candida albicans* and *Aspergillus flavus* [28,30]. In contrast, Gram-negative pathogens, including *Escherichia coli*, *Salmonella* Enteritidis, and *Salmonella* Typhimurium, have shown higher resistance to the essential oil [27,29], indicating a more selective antimicrobial spectrum [31].

While most previous phytochemical studies of *A. foeniculum* have focused on its essential oil composition [8,13,15,24,32], the analysis of non-volatile polar constituents has remained limited. Among the few studies utilizing methanolic extracts [33], Shanaida et al. [20] applied UHPLC-DAD-MS/MS to identify 9 secondary metabolites in the aerial

parts of the plant. Building on this, our study employed high-resolution UHPLC-MS/MS combined with organ-specific sampling (leaves and flowers) to achieve a more comprehensive and differentiated profiling of polar secondary metabolites. This approach extends current knowledge of the species' phytochemistry beyond its volatile constituents and contributes to the evaluation of *A. foeniculum* as a pharmacologically valuable resource.

Despite growing evidence for the antimicrobial properties of *A. foeniculum*, particularly against Gram-positive bacteria and some fungi, studies involving clinically relevant human pathogens remain scarce, and no investigations have yet addressed their efficacy against multidrug-resistant (MDR) bacterial strains, an urgent gap our study aims to fill.

2. Materials and Methods

2.1. Plant Material and Extraction

A. foeniculum plants were cultivated in the Medicinal and Herb Garden of the Institute of Agricultural and Engineering Sciences, University of Nyíregyháza (Hungary). Plant material was collected at full flowering on 20 July. Leaves and flowers were harvested from ten plants growing in the same raised bed and pooled to obtain representative samples for phytochemical and antimicrobial analyses. The plant material is part of the botanical garden collection. Species identification was confirmed by two co-authors, botanists Oleh Kolesnyk and Judit Csabai.

2.2. UHPLC-MS/MS Analysis

Plant tissues (leaves and flowers) were washed with distilled water, air-dried, and ground to a fine powder using a laboratory mill. Samples were stored at −20 °C until analysis.

For phytochemical analysis, 2 g of dried material was extracted in 50 mL of 70% methanol (v/v) at room temperature (~22 °C) for 2 h on a horizontal shaker (150 rpm). Extracts were filtered through 0.22 µm PTFE syringe filters prior to chromatographic injection.

The metabolite profile was analyzed by ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (UHPLC-MS/MS). Analyses were performed using a Dionex Ultimate 3000RS UHPLC system (Thermo Scientific, Waltham, MA, USA) equipped with a Phenomenex Kinetex XB-C18 column (Phenomenex, Torrance, CA, USA; 100 mm × 2.1 mm, 2.6 µm particle size), maintained at 25 ± 1 °C.

The mobile phases consisted of 0.1% formic acid in water (A) and methanol (B). The gradient elution was programmed as follows: 0–3 min, 95% A; 3–43 min, linear decrease to 0% A; 43–61 min, 0% A; 61–62 min, re-equilibration to 95% A; 62–70 min, 95% A. The flow rate was set at 200 µL/min.

Mass detection was conducted using a Q Exactive Orbitrap mass spectrometer (Thermo Scientific, Waltham, MA, USA) equipped with an electrospray ionization (ESI) source, operated in both positive and negative ion modes. Full scan spectra were acquired at 70,000 resolution, and MS/MS spectra at 35,000 resolution with normalized collision energy (NCE) of 30, in the m/z range of 100–1500.

Metabolite identification was based on accurate mass, isotopic pattern, diagnostic fragments, and retention time, using in-house and public spectral databases (METLIN, MassBank of North America, mzCloud). All compounds were confirmed with mass error <5 ppm using TraceFinder 3.1 software (Thermo Scientific, Waltham, MA, USA).

2.3. Antimicrobial Assay

While solvent-related differences may affect the exact composition of the extracts, the use of ethanol instead of methanol in antimicrobial assays was considered more appropriate to avoid potential toxicity-related interference with microbial viability. This approach was chosen to ensure more reliable biological results.

The dried plant material was extracted using 70% ethanol at room temperature, followed by filtration and solvent removal under reduced pressure [34]. The extraction was performed at a plant material-to-solvent ratio of 1:10 (w/v). The antimicrobial activity of ethanolic extracts was evaluated in Mueller–Hinton broth (MHB; HiMedia, Thane, India).

Test cultures. Multidrug-resistant clinical bacterial isolates were obtained from wound swabs of patients at the Uzhhorod City Multidisciplinary Clinical Hospital (Ukraine). Bacterial species included *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Citrobacter freundii*, *Achromobacter xylosoxidans*, and *Acinetobacter baumannii*.

The broth dilution method was used to determine antimicrobial activity.

The reconstituted extracts were tested at seven concentrations: 12.5% (18.75 mg/mL), 25% (37.5 mg/mL), 37.5% (56.25 mg/mL), 50% (75.0 mg/mL), 62.5% (93.75 mg/mL), 75% (112.5 mg/mL), and 87.5% (131.25 mg/mL) in sterile 96-well microplates containing Mueller–Hinton broth. Extract concentrations are expressed as percentage dilutions of the stock solution. Each well contained 90 µL of extract dilution and 10 µL of microbial suspension standardized to 0.5 McFarland (1.5×10^8 CFU/mL). Growth control (medium without extract) and solvent control were included. Plates were incubated at 37 °C for 24 h. Following incubation, 10 µL aliquots from each well were plated onto HM Peptone Agar (HiMedia, India), and colony formation was evaluated after an additional 24 h of incubation. Cases where no colonies were observed in the plated aliquot were considered below the detection limit of the assay. At high bacterial densities, samples were diluted as necessary prior to plating to obtain countable colony numbers for CFU determination, following routine microbiological practice. The antibacterial activity of the extracts was assessed by determining the number of surviving colony-forming units (CFU) [35].

3. Results

3.1. Secondary Metabolite Profile

In total, 54 secondary metabolites were identified in the extracts of *A. foeniculum* leaves and flowers. Of these, 50 compounds were detected in the leaves and 46 in the flowers. Seven metabolites were unique to the leaves, while three occurred exclusively in the flowers. The remaining 43 compounds were common to both plant organs (Tables A1 and A2).

Specifically, the following compounds were detected in the leaves but not in the flowers: neochlorogenic acid (5-O-caffeoylquinic acid), caftaric acid (2-O-caffeoyltartaric acid), agastenol, naringenin-6,8-di-C-glucoside, eugenol (4-allyl-2-methoxyphenol), methoxy-trihydroxy(iso)flavone isomer 2, and chrysoeriol-O-caffeoylhexoside (Table A1).

Conversely, the following metabolites were found exclusively in the flowers: phloretin (dihydronaringenin), dimethoxy-trihydroxy(iso)flavone, and hydroxy-tetramethoxy(iso) flavone (Table A2).

Analysis was performed using total ion chromatograms (TIC), which showed that the highest relative intensity for negative ions was observed for quinic acid in leaves and rosmarinic acid in flowers (Figure 1, Table 1). For positive ions, it was not possible to determine the compound with the highest peak intensity, as the TIC values for these analytes exceeded the upper detection limit of the UHPLC-MS/MS method.

Within the identified TIC-positive ion range, the compound with the highest relative intensity was tilianin (acacetin-7-O-glucoside) in leaves and pulegone in flowers (Table 1). In contrast, the TIC-negative ion range revealed a significantly greater number of compounds. In the leaf extracts, the following compounds showed the highest relative concentrations (in descending order): quinic acid, dihydroxy-methoxy(iso)flavone isomer 2, dihydroxy-dimethoxy(iso)flavone, citric acid, rosmarinic acid, dihydroxy-methoxy(iso)flavone isomer 3, 12-hydroxyjasmonic acid-12-O-glucoside (or tuberonic acid glucoside), and 4-O-glucosyl-4-hydroxycinnamate (Table 1).

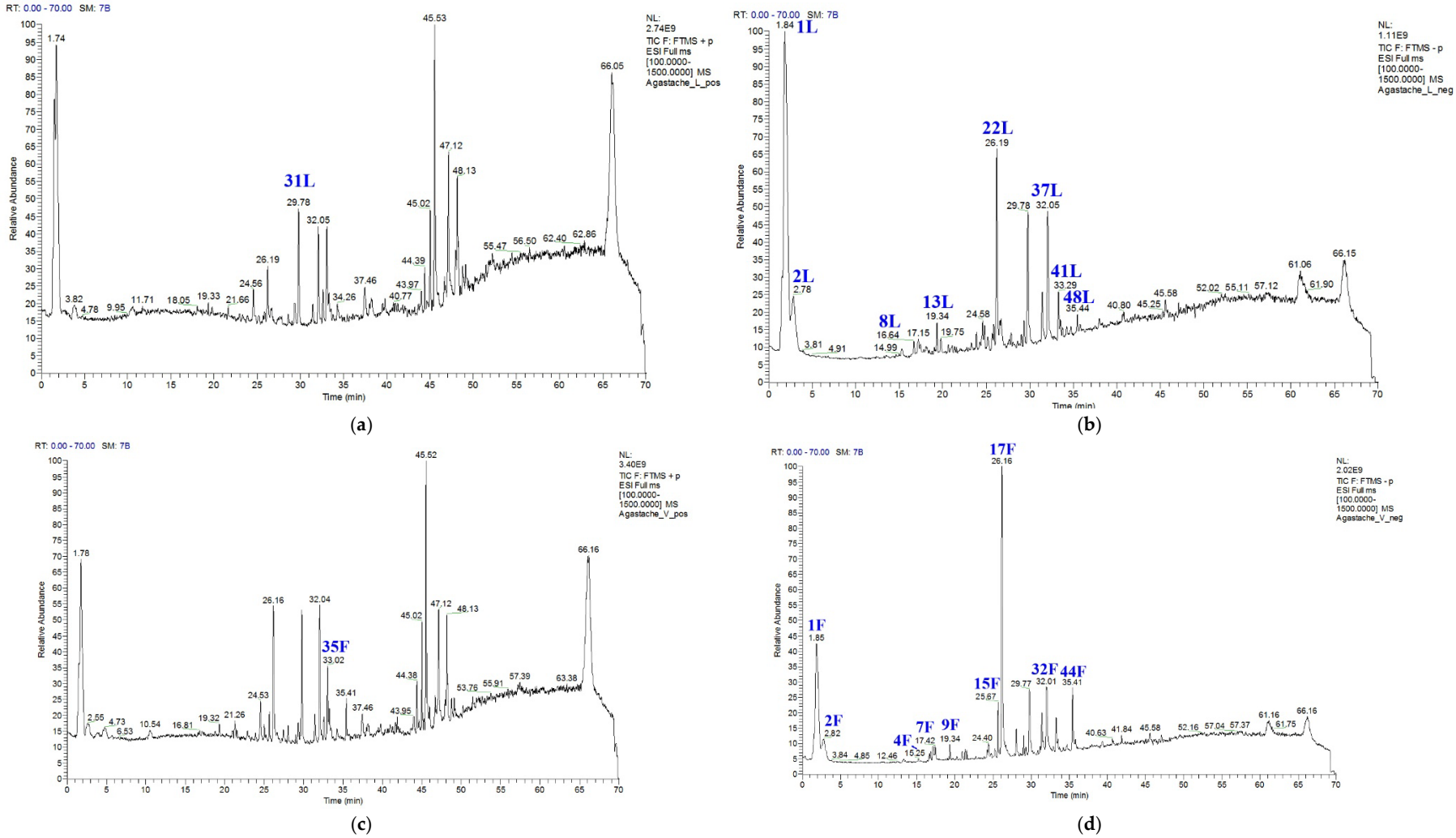

Figure 1. Total ion chromatograms (TIC) of *Agastache foeniculum* (Pursh) Kuntze extracts obtained by UHPLC-MS/MS. (**a**) Leaves—positive ion mode; (**b**) Leaves—negative ion mode; (**c**) Flowers—positive ion mode; (**d**) Flowers—negative ion mode. Blue peaks correspond to identified secondary metabolites; peak numbers refer to compounds listed in Tables A1 and A2. ("L"—leaves, "F"—flowers).

Table 1. Relative content of secondary metabolites identified in leaf and flower extracts of *Agastache foeniculum* (Pursh) Kuntze ("L"—leaves, "F"—flowers).

№	Name of Identified Compounds	Relative Abundance (%)			
		Leaves		Flowers	
		TIC^+	TIC^-	TIC^+	TIC^-
1L, 1F	Quinic acid		100		42.8
2L, 2F	Citric acid		24.6		11.5
4F	Salicylic acid-2-O-glucoside				5.1
7F	Caffeic acid				9.0
8L	4-O-Glucosyl-4-hydroxycinnamate		11.9		
13L, 9F	12-Hydroxyjasmonic acid-12-O-glucoside or Tuberonic acid glucoside		17.0		9.9
15F	Phlorizin (Phloretin-2′-O-glucoside)				23.6
22L, 17F	Rosmarinic acid		22.0		100
31L	Tilianin (Acacetin-7-O-glucoside)	47.7			
35F	Pulegone			35.7	
37L, 32F	Dihydroxy-methoxy(iso)flavone isomer 2		48.9		28.7
41L	Dihydroxy-dimethoxy(iso)flavone		25.9		
48L, 44F	Dihydroxy-methoxy(iso)flavone isomer 3		19.5		28.2

Note: The substance with the highest content is taken as 100%.

In the flower extracts, the most abundant negative-ion compounds included rosmarinic acid, quinic acid, dihydroxy-methoxy(iso)flavone isomer 2, dihydroxy-methoxy(iso)flavone isomer 3, phlorizin (phloretin-2′-O-glucoside), citric acid, 12-hydroxyjasmonic acid-12-O-glucoside (or tuberonic acid glucoside), caffeic acid, and salicylic acid-2-O-glucoside (Table 1).

As demonstrated by the above-mentioned compounds with the highest relative abundance, the phytochemical profile of *A. foeniculum* is primarily composed of organic acids and flavonoids. However, both the presence and relative concentration of these metabolites vary between the leaves and flowers. These organ-specific differences should be carefully considered when selecting plant material for nutritional or medicinal purposes.

3.2. Microbial Analysis

The ethanolic leaf extract of *A. foeniculum* exhibited concentration-dependent antibacterial effects against multidrug-resistant (MDR) clinical isolates, with the most pronounced activity generally observed at the highest tested concentration (87.5%) (Table 2). For *S. aureus*, bacterial survival decreased markedly from $5.0 \pm 0.2 \times 10^8$ CFU/mL in the control to below the detection limit at concentrations of 75% and 87.5%, indicating strong antibacterial activity.

For *C. freundii*, *A. xylosoxidans*, and *A. baumannii*, a gradual concentration-dependent reduction in bacterial counts was observed. At the highest tested concentration (87.5%), bacterial counts for all three strains were reduced below the detection limit of the assay. These findings indicate considerable antibacterial activity of the extract against Gram-negative MDR strains, particularly at higher concentrations.

E. faecalis showed moderate susceptibility, with the strongest inhibitory effect observed at 87.5%, where bacterial counts were also reduced below the detection limit of the assay (Table 2).

In the case of *E. coli*, bacterial counts progressively decreased with increasing extract concentration, reaching levels below the detection limit of the assay at 87.5% (Table 2).

Table 2. Antibacterial activity of *Agastache foeniculum* (Pursh) Kuntze leaf extract against multidrug-resistant clinical isolates (n = 10 per strain). Values are expressed as colony-forming units (CFU/mL) of surviving bacteria.

Microorganism	Broth (Control) CFU/mL	Broth + Extract						
		12.5% 18.75 mg/mL	25% 37.5 mg/mL	37.5% 56.25 mg/mL	50% 75 mg/mL	62.5% 93.75 mg/mL	75% 112.5 mg/mL	87.5% 131.25 mg/mL
Staphylococcusaureus	5.0 $\pm 0.2 \times 10^8$	8.0 $\pm 0.3 \times 10^6$	7.2 $\pm 0.2 \times 10^6$	5.9 $\pm 0.1 \times 10^6$	4.8 $\pm 0.5 \times 10^5$	3.0 $\pm 0.7 \times 10^5$	«-»	«-»
Citrobacter freundii	4.8 $\pm 0.3 \times 10^8$	8.4 $\pm 0.1 \times 10^6$	7.5 $\pm 0.3 \times 10^6$	6.8 $\pm 0.4 \times 10^6$	5.4 $\pm 0.3 \times 10^6$	4.1 $\pm 0.4 \times 10^6$	2.9 $\pm 0.8 \times 10^6$	«-»
Escherichia coli	5.0 $\pm 0.1 \times 10^8$	6.9 $\pm 0.5 \times 10^6$	5.1 $\pm 0.7 \times 10^6$	3.7 $\pm 0.6 \times 10^6$	2.1 $\pm 0.2 \times 10^6$	5.6 $\pm 0.2 \times 10^5$	4.7 $\pm 0.3 \times 10^4$	«-»
Achromobacter xylosoxidans	5.1 $\pm 0.2 \times 10^8$	8.4 $\pm 0.3 \times 10^6$	7.3 $\pm 0.2 \times 10^6$	6.4 $\pm 0.6 \times 10^6$	4.9 $\pm 0.7 \times 10^6$	3.1 $\pm 0.7 \times 10^6$	2.1 $\pm 0.8 \times 10^6$	«-»
Acinetobacter baumannii	4.9 $\pm 0.3 \times 10^8$	7.2 $\pm 0.2 \times 10^6$	6.4 $\pm 0.6 \times 10^6$	5.1 $\pm 0.5 \times 10^6$	3.9 $\pm 0.2 \times 10^6$	2.4 $\pm 0.5 \times 10^6$	1.5 $\pm 0.6 \times 10^6$	«-»
Enterococcus faecalis	4.7 $\pm 0.4 \times 10^8$	6.7 $\pm 0.3 \times 10^6$	5.4 $\pm 0.6 \times 10^6$	3.9 $\pm 0.7 \times 10^6$	5.6 $\pm 0.5 \times 10^5$	4.3 $\pm 0.5 \times 10^5$	2.9 $\pm 0.6 \times 10^5$	«-»

«-»—no colonies detected in the plated aliquot (below the detection limit of the assay).

Overall, the leaf extract demonstrated concentration-dependent inhibitory activity against all tested bacterial strains.

The flower extract of *A. foeniculum* exhibited concentration-dependent antibacterial activity against multidrug-resistant (MDR) clinical isolates, with the strongest inhibitory effects generally observed at 62.5–87.5% concentrations (Table 3).

Table 3. Antibacterial activity of *Agastache foeniculum* (Pursh) Kuntze flower extract against multidrug-resistant clinical isolates (n = 10 per strain). Values are expressed as colony-forming units (CFU/mL) of surviving bacteria.

Microorganism	Broth (Control) CFU/mL	Broth + Extract						
		12.5% 18.75 mg/mL	25% 37.5 mg/mL	37.5% 56.25 mg/mL	50% 75 mg/mL	62.5% 93.75 mg/mL	75% 112.5 mg/mL	87.5% 131.25 mg/mL
Staphylococcus aureus	5.0 $\pm 0.2 \times 10^8$	4.2 $\pm 0.5 \times 10^6$	3.1 $\pm 0.4 \times 10^4$	1.4 $\pm 0.5 \times 10^3$	«-»	«-»	«-»	«-»
Citrobacter freundii	4.8 $\pm 0.3 \times 10^8$	7.4 $\pm 0.4 \times 10^6$	6.2 $\pm 0.3 \times 10^6$	5.8 $\pm 0.4 \times 10^6$	4.3 $\pm 0.3 \times 10^6$	3.8 $\pm 0.4 \times 10^5$	3.1 $\pm 0.3 \times 10^5$	«-»
Escherichia coli	5.0 $\pm 0.1 \times 10^8$	6.4 $\pm 0.5 \times 10^6$	4.8 $\pm 0.4 \times 10^6$	3.2 $\pm 0.4 \times 10^6$	1.8 $\pm 0.4 \times 10^6$	1.0 $\pm 0.4 \times 10^5$	0.5 $\pm 0.2 \times 10^4$	«-»
Achromobacter xylosoxidans	5.1 $\pm 0.2 \times 10^8$	7.4 $\pm 0.4 \times 10^6$	6.2 $\pm 0.3 \times 10^6$	5.1 $\pm 0.3 \times 10^6$	3.9 $\pm 0.7 \times 10^6$	3.2 $\pm 0.4 \times 10^5$	2.1 $\pm 0.3 \times 10^5$	4.1 $\pm 0.2 \times 10^2$
Acinetobacter baumannii	4.9 $\pm 0.3 \times 10^8$	5.3 $\pm 0.4 \times 10^6$	4.1 $\pm 0.6 \times 10^6$	2.7 $\pm 0.7 \times 10^6$	1.6 $\pm 0.4 \times 10^6$	«-»	«-»	«-»
Enterococcus faecalis	4.7 $\pm 0.4 \times 10^8$	5.6 $\pm 0.7 \times 10^5$	4.2 $\pm 0.6 \times 10^5$	2.8 $\pm 0.7 \times 10^5$	1.2 $\pm 0.3 \times 10^3$	1.3 $\pm 0.7 \times 10^2$	«-»	«-»

«-»—no colonies detected in the plated aliquot (below the detection limit of the assay).

S. aureus and *A. baumannii* were the most susceptible strains, with no colonies detected in the plated aliquots at higher extract concentrations. *C. freundii*, *E. coli*, and *A. xylosoxidans* also demonstrated progressive reductions in viable bacterial counts with increasing extract concentration.

E. faecalis showed moderate susceptibility, with the greatest reduction observed at the highest tested concentrations. Overall, the flower extract demonstrated substantial antibacterial activity against all tested MDR bacterial strains.

4. Discussion

One of the most significant outcomes of our study is the identification of 35 previously unreported secondary metabolites in the flower extract and 38 in the leaf extract of *A. foeniculum*. This number substantially exceeds those reported in earlier studies employing either essential oil analysis [8,15,32] or methanolic extractions [20,33]. While previous research has focused primarily on volatile constituents or non-differentiated plant material, our application of high-resolution UHPLC-MS/MS combined with organ-specific sampling enabled a more comprehensive and resolved characterization of polar secondary metabolites. This approach provides new insights into the metabolic specialization of different plant organs, which is often overlooked in phytochemical studies.

The markedly higher number of detected compounds suggests that the phytochemical complexity of *A. foeniculum* has been substantially underestimated, particularly with regard to its non-volatile constituents. This expanded metabolite coverage is essential for a more accurate evaluation of the species' biological potential and may contribute to improved standardization and targeted utilization of plant-derived products.

Although several studies have demonstrated the antimicrobial activity of *A. foeniculum*, the available literature remains limited in scope. Most studies have focused on essential oils and a narrow range of standard laboratory strains, typically using disc diffusion assays [8,27–29]. In contrast, the present study employed ethanolic extracts and evaluated antibacterial activity using CFU-based quantification against clinical multidrug-resistant (MDR) isolates. This approach may provide a broader assessment of antimicrobial potential against clinically relevant MDR isolates. Notably, several of the tested species (*A. baumannii*, *A. xylosoxidans*, *C. freundii* and *E. faecalis*) have not previously been investigated in relation to *A. foeniculum*, further extending the current knowledge base.

The requirement for relatively high extract concentrations to achieve substantial antibacterial effects may reflect the intrinsic resistance mechanisms of MDR strains, as well as the complex, multi-component nature of plant extracts, where synergistic and antagonistic interactions can influence overall activity [36].

The generally higher antibacterial activity of the flower extract compared to the leaf extract is likely associated with both qualitative and quantitative differences in their phytochemical composition. The presence of unique compounds, such as phloretin [37,38], together with higher relative levels of shared phenolic constituents (e.g., rosmarinic and caffeic acids), may contribute to the enhanced bioactivity.

In contrast to tannin-rich plant extracts, where antibacterial activity is often driven by nonspecific protein precipitation [39], the activity observed here may involve more specific interactions of phenolic compounds with bacterial targets. These findings suggest that organ-specific metabolite composition plays a key role in determining the antibacterial efficacy of *A. foeniculum* extracts.

It is also noteworthy that certain abundant compounds in the flower extract, such as pulegone, are known constituents of essential oils. Due to their higher solubility in lipophilic matrices, essential oil preparations of *A. foeniculum*, which concentrate such volatile compounds, may exhibit enhanced antimicrobial activity.

These observations suggest that combining polar and non-polar extraction approaches may provide a broader representation of the plant's bioactive constituents.

5. Conclusions

Our results demonstrate that *A. foeniculum* possesses a more complex secondary metabolite profile than previously described, with 35 and 38 compounds not previously reported in the flower and leaf extracts, respectively. These phytochemical insights are essential for understanding the pharmacological potential of the species and lay the founda-

tion for future bioactivity-guided studies. Importantly, the antibacterial activity observed, particularly against multidrug-resistant human pathogens, suggests that *A. foeniculum* could serve as a valuable reservoir of novel antimicrobial agents. The organ-specific efficacy, especially the superior activity of the flower extract, highlights the importance of targeted extraction strategies in future plant-based antimicrobial research.

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Data Availability Statement: The data supporting the findings of this study are available upon reasonable request. Plant material documentation and UHPLC-MS/MS raw and processed data are archived at the University of Nyíregyháza (Hungary). Microbiological assay data are stored at Uzhhorod National University (Ukraine).

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Abbreviations

The following abbreviations are used in this manuscript:

BBCH	Biologische Bundesanstalt, Bundessortenamt and Chemical Industry growth scale
CFU	Colony-forming unit
EO	Essential oil
ESI	Electrospray ionization
GC–MS	Gas chromatography–mass spectrometry
MDR	Multidrug-resistant
ME	Methanolic extract
MS/MS	Tandem mass spectrometry
NCE	Normalized collision energy
PTFE	Polytetrafluoroethylene
Rt	Retention time
SAR	Structure–activity relationship
TIC	Total ion chromatogram
UHPLC	Ultra-high-performance liquid chromatography
UHPLC-MS/MS	Ultra-high-performance liquid chromatography coupled with tandem mass spectrometry

Appendix A

Table A1. Secondary metabolite composition of *Agastache foeniculum* (Pursh) Kuntze leaf extracts (Fragment 1–5 indicate the main MS/MS fragment ions used for compound identification).

No.	Name	Formula	Rt	$[M + H]^+$	$[M - H]^-$	Fragment 1	Fragment 2	Fragment 3	Fragment 4	Fragment 5	Literature
1	Quinic acid	$C_7H_{12}O_6$	1.85		191.05557	173.0448	171.0292	127.0389	111.0437	93.0332	
2	Citric acid	$C_6H_8O_7$	2.78		191.01918	173.0081	129.0182	111.0074	87.0073	85.0280	
3 [1]	Neochlorogenic acid (5-O-Caffeoylquinic acid)	$C_{16}H_{18}O_9$	13.48	355.10291		163.0391	145.0287	135.0444	117.0336	89.0393	
4	Caftaric acid (2-O-Caffeoyltartaric acid)	$C_{13}H_{12}O_9$	14.24		311.04031	179.0343	149.0081	135.0441	87.0073		
5	Feruloylputrescine	$C_{14}H_{20}N_2O_3$	14.44	265.15522		248.1283	177.0548	145.0287	117.0338		
6	Salicylic acid-2-O-glucoside	$C_{13}H_{16}O_8$	15.25		299.07670	137.0233	113.0231	93.0331	85.0282	71.0123	
7	Agastenol	$C_{27}H_{26}O_8$	16.58		477.15495	341.0889	281.0671	251.0558	221.0453	179.0343	
8	4-O-Glucosyl-4-hydroxycinnamate	$C_{15}H_{18}O_8$	16.63		325.09235	163.0390	119.0489				
9 [1]	Chlorogenic acid (3-O-Caffeoylquinic acid)	$C_{16}H_{18}O_9$	17.14	355.10291		163.0392	145.0287	135.0443	117.0339	89.0391	[20] ME
10 [1]	Caffeic acid	$C_9H_8O_4$	17.43		179.03444	135.0440	107.0489				[20] ME [15] EO
11 [1]	Chryptochlorogenic acid (4-O-Caffeoylquinic acid)	$C_{16}H_{18}O_9$	17.97	355.10291		163.0392	145.0287	135.0444	117.0340	89.0391	
12	Naringenin-6,8-di-C-glucoside	$C_{27}H_{32}O_{15}$	18.57		595.16630	475.1261	415.1054	385.0948	355.0835	313.0728	
13	12-Hydroxyjasmonic acid-12-O-glucoside or Tuberonic acid glucoside	$C_{18}H_{28}O_9$	19.34		387.16551	225.1133	207.1025	101.0231	89.0229	59.0124	
14	5-O-(4-Coumaroyl)quinic acid	$C_{16}H_{18}O_8$	19.66		337.09235	191.0557	173.0448	163.0387	119.0490		
15 [1]	p-Coumaric acid	$C_9H_8O_3$	20.58		163.03952	119.0489					[15] EO
16	Phaselic acid (2-O-Caffeoylmalic acid)	$C_{13}H_{12}O_8$	20.63		295.04540	179.0343	135.0441	133.0131	115.0023	71.0123	
17	Vicenin-2 (Apigenin-6,8-di-C-glucoside)	$C_{27}H_{30}O_{15}$	20.73	595.16630		577.1497	457.1134	337.0707	325.0710	295.0604	
18	Rosmarinic acid glucoside	$C_{24}H_{26}O_{13}$	24.76		521.12952	359.0776	323.0776	197.0450	179.0343	161.0234	
19	Eugenol (4-Allyl-2-methoxyphenol)	$C_{10}H_{12}O_2$	25.13	165.09156		137.0600	133.0651	124.0522	109.0288	105.0704	[13] EO
20 [1]	Phlorizin (Phloretin-2′-O-glucoside)	$C_{21}H_{24}O_{10}$	25.67		435.12913	273.0774	179.0343	167.0340	125.0232	123.0439	
21 [1]	Cosmosin (Apigenin-7-O-glucoside)	$C_{21}H_{20}O_{10}$	26.07	433.11347		271.0603	153.0184				[20] ME
22	Rosmarinic acid	$C_{18}H_{16}O_8$	26.19		359.07670	197.0451	179.0343	161.0234	135.0441	72.9916	[20] ME [33] ME
23	Methoxy-trihydroxy(iso)flavone isomer 1	$C_{16}H_{12}O_6$	26.67		299.05556	284.0332	256.0371				
24	Luteolin-O-malonylhexoside	$C_{24}H_{22}O_{14}$	27.62		533.09314	489.1046	447.0932	285.0409	284.0331	133.0280	
25	2-(p-Coumaroyl)-3-(3,4-dihydroxyphenyl)propanoic acid	$C_{18}H_{16}O_7$	27.83		343.08178	197.0454	179.0344	145.0286	135.0439	72.9918	
26	3-O-Methylrosmarinic acid	$C_{19}H_{18}O_8$	28.07		373.09235	197.0452	179.0346	175.0392	160.0155	135.0441	
27	Methoxy-trihydroxy(iso)flavone isomer 2	$C_{16}H_{12}O_6$	28.51		299.05556	284.0330					

Table A1. *Cont.*

No.	Name	Formula	Rt	[M + H]$^+$	[M − H]$^-$	Fragment 1	Fragment 2	Fragment 3	Fragment 4	Fragment 5	Literature
28	Di-O-(p-coumaroyl)hexose	$C_{24}H_{24}O_{10}$	28.56		471.12913	307.0823	163.0389	145.0284	119.0489		
29	Apigenin-O-acetylhexoside	$C_{23}H_{22}O_{11}$	29.00		473.10839	269.0459	268.0382	151.0025	117.0329		
30	Chrysoeriol-O-malonylhexoside	$C_{25}H_{24}O_{14}$	29.32	549.12443		505.1330	463.1249	301.0708	286.0473	258.0519	
31	Tilianin (Acacetin-7-O-glucoside)	$C_{22}H_{22}O_{10}$	29.78	447.12913		285.0760	270.0526	242.0569			[33] [ME]
32 [1]	Luteolin (3′,4′,5,7-Tetrahydroxyflavone)	$C_{15}H_{10}O_6$	30.18		285.03991	151.0017	133.0286				
33	Chrysoeriol-O-caffeoylhexoside	$C_{31}H_{28}O_{14}$	30.64		623.14009	323.0771	299.0579	284.0331	179.0342	161.0234	
34	Dihydroxy-methoxy(iso)flavone isomer 1	$C_{16}H_{12}O_5$	31.41		283.06065	268.0381	240.0426	239.0341	211.0394	151.0029	
35	Dimethoxy-trihydroxy(iso)flavone	$C_{17}H_{14}O_7$	31.63		329.06613	314.0440	313.0359	299.0203	285.0403	271.0254	
36 [1]	Apigenin (4′,5,7-Trihydroxyflavone)	$C_{15}H_{10}O_5$	31.90		269.04500	225.0572	151.0026	149.0234	117.0332		[20] [ME]
37	Dihydroxy-methoxy(iso)flavone isomer 2	$C_{16}H_{12}O_5$	32.05		283.06065	268.0381	240.0424	239.0347	211.0393	151.0027	
38	Spathulenol	$C_{15}H_{24}O$	32.15	221.19055		203.1799	163.1488	161.1329	147.1169	107.0861	[13] [EO]
39	Chrysoeriol (3′-Methoxy-4′,5,7-trihydroxyflavone)	$C_{16}H_{12}O_6$	32.20		299.05556	284.0329	256.0384				
40	Pulegone	$C_{10}H_{16}O$	33.03	153.12795		135.1170	109.1016	107.0860	93.0704	81.0705	[32] [EO]
41	Dihydroxy-dimethoxy(iso)flavone	$C_{17}H_{14}O_6$	33.29		313.07122	298.0486	297.0409	283.0252	269.0458	255.0300	
42	Dihydroxy-trimethoxy(iso)flavone	$C_{18}H_{16}O_7$	33.39	345.09743		330.0736	315.0514	312.0628	284.0679	269.0447	
43	Malyngic acid (9,12,13-Trihydroxy-10E,15Z-octadecadienoic acid)	$C_{18}H_{32}O_5$	33.48		327.21715	309.2066	291.1972	229.1443	211.1335	171.1017	
44	Isoagastachoside (Acacetin-7-O-(2″-O-acetyl)glucoside)	$C_{24}H_{24}O_{11}$	33.73	489.13969		285.0759	270.0529	242.0582			
45	Isomenthone	$C_{10}H_{18}O$	33.88	155.14360		137.1327	95.0861	81.0705	69.0706	55.0550	[32] [EO]
46	Methoxy-trihydroxy(iso)flavone isomer 3	$C_{16}H_{12}O_6$	34.03		299.05556	284.0328					
47	Pinellic acid (9,12,13-Trihydroxy-10E-octadecenoic acid)	$C_{18}H_{34}O_5$	34.68		329.23280	311.2242	293.2124	229.1441	211.1335	99.0801	
48	Dihydroxy-methoxy(iso)flavone isomer 3	$C_{16}H_{12}O_5$	35.44		283.06065	268.0380	267.0294	240.0423	239.0346	211.0388	
49	Acacetin (5,7-Dihydroxy-4′-methoxyflavone)	$C_{16}H_{12}O_5$	35.79		283.06065	268.0381	267.0294	240.0417	239.0345	151.0028	[33] [ME]
50	Hydroxy-trimethoxy(iso)flavone	$C_{18}H_{16}O_6$	36.47	329.10251		314.0787	296.0683	268.0726	240.0781		

[1] Confirmed by standard; [EO]: essential oil (data from literature); [ME]: methanolic extract (data from literature).

Table A2. Chemical composition of flower extracts from *Agastache foeniculum* (Pursh) Kuntze (Fragment 1–5 indicate the main MS/MS fragment ions used for compound identification).

No.	Name	Formula	Rt	$[M + H]^+$	$[M - H]^-$	Fragment 1	Fragment 2	Fragment 3	Fragment 4	Fragment 5	Literature
1	Quinic acid	$C_7H_{12}O_6$	1.83		191.05557	173.0447	171.0288	127.0388	111.0438	93.0334	
2	Citric acid	$C_6H_8O_7$	2.82		191.01918	173.0084	129.0182	111.0074	87.0073	85.0280	
3	Feruloylputrescine	$C_{14}H_{20}N_2O_3$	14.43	265.15522		248.1281	177.0548	145.0287	117.0334		
4	Salicylic acid-2-O-glucoside	$C_{13}H_{16}O_8$	15.23		299.07670	137.0233	113.0231	93.0331	85.0280	71.0123	
5	4-O-Glucosyl-4-hydroxycinnamate	$C_{15}H_{18}O_8$	16.61		325.09235	163.0390	119.0489				
6 [1]	Chlorogenic acid (3-O-Caffeoylquinic acid)	$C_{16}H_{18}O_9$	17.12	355.10291		163.0392	145.0288	135.0444	117.0339	89.0390	[20] ME
7 [1]	Caffeic acid	$C_9H_8O_4$	17.42		179.03444	135.0440	107.0487				[20] ME [15] EO
8 [1]F	Chryptochlorogenic acid (4-O-Caffeoylquinic acid)	$C_{16}H_{18}O_9$	17.97	355.10291		163.0391	145.0286	135.0444	117.0339	89.0393	
9F	12-Hydroxyjasmonic acid-12-O-glucoside or Tuberonic acid glucoside	$C_{18}H_{28}O_9$	19.34		387.16551	225.1123	207.1023	101.0230	89.0229	59.0123	
10F	5-O-(4-Coumaroyl)quinic acid	$C_{16}H_{18}O_8$	19.66		337.09235	191.0556	173.0446	163.0391	119.0489		
11 [1]F	p-Coumaric acid	$C_9H_8O_3$	20.58		163.03952	119.0489					[15] EO
12F	Phaselic acid (2-O-Caffeoylmalic acid)	$C_{13}H_{12}O_8$	20.63		295.04540	179.0344	135.0441	133.0132	115.0025	71.0124	
13F	Vicenin-2 (Apigenin-6,8-di-C-glucoside)	$C_{27}H_{30}O_{15}$	20.73	595.16630		577.1563	457.1124	337.0706	325.0705	295.0608	
14F	Rosmarinic acid glucoside	$C_{24}H_{26}O_{13}$	24.74		521.12952	359.0772	323.0779	197.0452	179.0343	161.0234	
15 [1]F	Phlorizin (Phloretin-2′-O-glucoside)	$C_{21}H_{24}O_{10}$	25.67		435.12913	273.0774	179.0343	167.0340	125.0232	123.0438	
16 [1]F	Cosmosiin (Apigenin-7-O-glucoside)	$C_{21}H_{20}O_{10}$	26.04	433.11347		271.0601	153.0182				[20] ME
17F	Rosmarinic acid	$C_{18}H_{16}O_8$	26.16		359.07670	197.0451	179.0343	161.0234	135.0441	72.9916	[20] ME [33] ME
18F	Methoxy-trihydroxy(iso)flavone isomer 1	$C_{16}H_{12}O_6$	26.66		299.05556	284.0334	256.0371				
19F	Luteolin-O-malonylhexoside	$C_{24}H_{22}O_{14}$	27.61		533.09314	489.1046	447.0952	285.0409	284.0331	133.0285	
20F	2-(p-Coumaroyl)-3-(3,4-dihydroxyphenyl)propanoic acid	$C_{18}H_{16}O_7$	27.82		343.08178	197.0453	179.0342	145.0284	135.0441	72.9917	
21F	3-O-Methylrosmarinic acid	$C_{19}H_{18}O_8$	28.05		373.09235	197.0450	179.0342	175.0391	160.0155	135.0440	
22F	Di-O-(p-coumaroyl)hexose	$C_{24}H_{24}O_{10}$	28.55		471.12913	307.0826	163.0390	145.0283	119.0489		
23F	Apigenin-O-acetylhexoside	$C_{23}H_{22}O_{11}$	28.99		473.10839	269.0459	268.0381	151.0024	117.0329		
24F	Chrysoeriol-O-malonylhexoside	$C_{25}H_{24}O_{14}$	29.32	549.12443		505.1327	463.1233	301.0710	286.0474	258.0523	
25F	Tilianin (Acacetin-7-O-glucoside)	$C_{22}H_{22}O_{10}$	29.77	447.12913		285.0759	270.0521	242.0570			[33] ME
26 [1]F	Phloretin (Dihydronaringenin)	$C_{15}H_{14}O_5$	29.97		273.07630	179.0349	167.0340	125.0231	123.0440	119.0490	
27 [1]F	Luteolin (3′,4′,5,7-Tetrahydroxyflavone)	$C_{15}H_{10}O_6$	30.16		285.03991	151.0023	133.0286				

Table A2. *Cont.*

No.	Name	Formula	Rt	[M + H]$^+$	[M − H]$^-$	Fragment 1	Fragment 2	Fragment 3	Fragment 4	Fragment 5	Literature
28F	Dihydroxy-methoxy(iso)flavanone	$C_{16}H_{14}O_5$	30.88		285.07630	270.0544	243.0661	164.0107	151.0026	136.0153	
29F	Dihydroxy-methoxy(iso)flavone isomer 1	$C_{16}H_{12}O_5$	31.41		283.06065	268.0381	240.0421	239.0345	211.0389	151.0024	
30F	Dimethoxy-trihydroxy(iso)flavone	$C_{17}H_{14}O_7$	31.61		329.06613	314.0437	313.0360	299.0202	285.0410	271.0251	
31 [1] F	Apigenin (4′,5,7-Trihydroxyflavone)	$C_{15}H_{10}O_5$	31.87		269.04500	225.0550	151.0026	149.0234	117.0332		[20] [ME]
32F	Dihydroxy-methoxy(iso)flavone isomer 2	$C_{16}H_{12}O_5$	32.01		283.06065	268.0380	240.0427	239.0347	211.0390	151.0026	
33F	Spathulenol	$C_{15}H_{24}O$	32.14	221.19055		203.1801	163.1483	161.1325	147.1169	107.0859	[13] [EO]
34F	Chrysoeriol (3′-Methoxy-4′,5,7-trihydroxyflavone)	$C_{16}H_{12}O_6$	32.18		299.05556	284.0330	256.0376				
35F	Pulegone	$C_{10}H_{16}O$	33.02	153.12795		135.1170	109.1016	107.0860	93.0704	81.0705	[32] [EO]
36F	Dihydroxy-dimethoxy(iso)flavone	$C_{17}H_{14}O_6$	33.27		313.07122	298.0487	297.0409	283.0253	269.0461	255.0299	
37F	Dihydroxy-trimethoxy(iso)flavone	$C_{18}H_{16}O_7$	33.39	345.09743		330.0733	315.0480	312.0629	284.0680	269.0443	
38F	Malyngic acid (9,12,13-Trihydroxy-10E,15Z-octadecadienoic acid)	$C_{18}H_{32}O_5$	33.47		327.21715	309.2078	291.1965	229.1441	211.1335	171.1019	
39F	Isoagastachoside (Acacetin-7-O-(2″-O-acetyl)glucoside)	$C_{24}H_{24}O_{11}$	33.73	489.13969		285.0760	270.0519	242.0566			
40F	Isomenthone	$C_{10}H_{18}O$	33.86	155.14360		137.1328	95.0861	81.0705	69.0706	55.0550	[32] [EO]
41F	Methoxy-trihydroxy(iso)flavone isomer 3	$C_{16}H_{12}O_6$	34.00		299.05556	284.0331	256.0373	151.0023	133.0286		
42F	Pinellic acid (9,12,13-Trihydroxy-10E-octadecenoic acid)	$C_{18}H_{34}O_5$	34.66		329.23280	311.2225	293.2127	229.1443	211.1335	99.0802	
43F	Hydroxy-tetramethoxy(iso)flavone	$C_{19}H_{18}O_7$	34.83	359.11308		344.0894	343.0809	326.0787	315.0866	298.0839	
44F	Dihydroxy-methoxy(iso)flavone isomer 3	$C_{16}H_{12}O_5$	35.41		283.06065	268.0380	267.0297	240.0430	239.0352	211.0396	
45F	Acacetin (5,7-Dihydroxy-4′-methoxyflavone)	$C_{16}H_{12}O_5$	35.78		283.06065	268.0380	267.0315	240.0425	239.0349	151.0028	[33] [ME]
46F	Hydroxy-trimethoxy(iso)flavone	$C_{18}H_{16}O_6$	36.50	329.10251		314.0794	296.0682	268.0733	240.0783		

[1] Confirmed by standard; [EO]: essential oil (data from literature); [ME]: methanolic extract (data from literature).

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