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# Chamazulene Content and Hypoglycemic Potential of *Matricaria chamomilla* L. Samples Collected from Six Different Localities of Diyarbakır/Türkiye

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**Abstract:** Chamomile (*Matricaria chamomilla* L.) is one of the oldest and most widely known medicinal plants belonging to Asteraceae family. An artifact named chamazulene forms from the sesquiterpene structured lactones such as matricin during the hydro-distillation of flowering tops of chamomile. These compounds are associated with the anti-inflammatory potential of chamomile along with flavonoids, other sesquiterpenoids, and essential oil of the plant. However, not all *M. chamomilla* specimens grown in different regions or species known and used as chamomile contains sesquiterpene lactone components. Thus, chamazulene content of chamomile has become a pharmaceutical interest. A traditional and well-established indication of the plant is diabetes. Protective and beneficial effects of chamomile on diabetic complications and glycemic control have been proposed by several studies. However, the mechanism of action is yet to be elucidated. Flowering tops of chamomile samples were collected from six different localities of Diyarbakır/Türkiye. Essential oils (EOs) were obtained by hydro-distillation. Petroleum ether (PE), ethyl acetate (EA), methanol (Me), and infusion (INF) extracts were prepared. Qualitative analysis of the EOs resulted in no chamazulene content. Bismil district might be eligible for medicinal chamomile culture with its high essential oil yield. *In-vitro* hypoglycemic potentials of the extracts and EOs were evaluated by α-glucosidase inhibitory assay. All EOs and EA extracts (except M4-Bismil samples) showed the highest inhibitory activities comparable to that of standard acarbose. α-Glucosidase inhibition might be a significant mechanism of action contributing to the antidiabetic effects of chamomile.

**Keywords:** Chamomile, sesquiterpene lactone, antidiabetic, α-Glucosidase.

## Diyarbakır/Türkiye'nin Altı Farklı Bölgesinden Toplanan *Matricaria chamomilla* L. Örneklerinin Kamazulen İçeriği ve Hipoglisemik Potansiyeli

**Öz:** Asteraceae familyasına ait olan papatya (*Matricaria chamomilla* L.), dünyanın en eski ve en çok bilinen tıbbi bitkilerinden birisidir. Papatyanın çiçekli dal uçlarının su distilasyonu sırasında matrisin gibi seskiterpen laktonlardan kamazulen isimli bir yan ürün oluşur. Bu bileşikler bitkinin flavonoidleri, diğer seskiterpenoidleri ve uçucu yağı ile birlikte papatyanın anti-enflamatuvar aktivitesiyle ilişkilendirilmektedir. Fakat farklı bölgelerde yetişen *M. chamomilla* örnekleri ya da papatya olarak bilinip kullanılan tüm türler seskiterpen lakton bileşik taşımazlar. Bu nedenle papatyaların kamazulen içeriği farmasötik açıdan ilgi çekmektedir. Diyabet, bitkinin geleneksel ve köklü endikasyonlarından birisidir. Papatyanın diyabetik komplikasyonlar ile glisemik kontrol üzerindeki koruyucu ve faydalı etkileri birçok çalışmada gösterilmiştir. Ancak etki mekanizması henüz aydınlatılamamıştır. Diyarbakır/Türkiye'nin altı farklı bölgesinden papatya çiçekli dal uçları toplanıp su distilasyonu ile uçucu yağları elde edilmiştir. Ayrıca petrol eteri (PE), etil asetat (EA), metanol (Me) ve infüzyon (INF) ekstreleri hazırlanmıştır. Uçucu yağların kalitatif analizi kamazulen taşımadıklarını göstermiştir. Bismil bölgesi yüksek uçucu yağ verimi ile tıbbi papatya kültürü için uygun olabilir. Ekstrelerin ve uçucu yağların hipoglisemik potansiyelleri *in-vitro* α-glukozidaz enzim inhibisyonu ile değerlendirilmiştir. Uçucu yağlar ve EA ekstreleri (M4-Bismil örnekleri hariç) en yüksek aktiviteyi göstermiştir ve bu aktivite standart akarboz ile kıyaslanabilir seviyededir. α-Glukozidaz inhibisyonu, papatyanın antidiyabetik etkisine önemli katkı sağlayan bir etki mekanizması olabilir.

**Anahtar kelimeler:** Papatya, seskiterpen lakton, antidiyabetik, α-Glukozidaz.

## 1. Introduction

Use of plants is as old as human history. These practices include utilizing plants as food source, animal feeding, firewood, building materials, and recreational, veterinary, culinary and medical purposes. One of the most widely known medicinal plants is *Matricaria chamomilla* L. (chamomile). This plant belongs to Asteraceae family and grows naturally in Asia, eastern and southern Europe, southern Africa, northwestern America, and the Mediterranean region. Chamomile has been known and used since the ancient civilizations such as Egypt, Greek, and Rome. Traditional indications of the herb include gastrointestinal, respiratory, liver, mouth-throat, urinary, menstrual, neuropsychiatric, skin, and eye diseases. Furthermore, antioxidant, antimicrobial, analgesic, antipyretic, antianxiety, antidepressant, sedative, antihypertensive, gastroprotective, antiparasitic, anti-inflammatory, antiphlogistic, and antidiabetic effects are some of the reported biological aspects of the plant. *M. chamomilla* is recorded in pharmacopoeias of more than 25 countries and it is valued for its flowers and essential oil obtained from flower-heads or flowering tops (fresh or dried) (El Mihyaoui et al., 2022; Hajizadeh-Sharafabad et al., 2020; Singh et al., 2011). Phytochemical composition of

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*M. chamomilla* consists of more than one hundred compounds belonging to several chemical classes such as flavonoid, sesquiterpenoid, coumarin, polyacetylene, and organic acid (Ali Esmail & Lawahidh Fali, 2023; El Mihyaoui et al., 2022). The essential oil of the plant is known for its characteristic blue color and composed of sesquiterpene compounds rather than monoterpenes. Main components of the essential oil were reported as β-farnesene, farnesol, α-bisabolol, bisabolol oxides, and chamazulene that is known as the responsible compound of the blue color. Chamazulene is an artifact formed from proazulenic sesquiterpene lactones (e.g., matricin) during the hydro-distillation of herbal material. Furthermore, this compound is a metabolite occurring after oral administration of pure matricin. There are many studies reporting the anti-inflammatory activities of both matricin and chamazulene. Therefore, the successful use of chamomile against inflammatory diseases in traditional medicine has been associated with the presence of these substances. However, all *M. chamomilla* specimens grown in different regions or all species known and used as chamomile do not contain sesquiterpene lactones. Thus, chamazulene content of chamomile has become a pharmaceutical interest (Flemming et al., 2015; Ghasemi et al., 2016; Ramadan et al., 2006; Wu et al., 2022).

Diabetes mellitus (DM) is a very common chronic disorder. This metabolic disease is usually characterized with hyperglycaemia and generally divided into four types: Type I, II, Gestational DM, which occurs only during pregnancy, and other types. Type II DM is noninsulin-dependent and it is the most common type of DM. DM and hyperglycaemia cause serious complications such as neuropathy, nephropathy, vascular and heart diseases in the long term. An important part of the treatment of Type II DM is preventing the postprandial glucose absorption (PPGA). FDA-approved α-glucosidase inhibitors such as acarbose, effect with this mechanism of action. These inhibitors prevent the hydrolysis of the polysaccharides to oligo- and monosaccharides in intestine (Apostolidis & Lee, 2010; Trinh et al., 2016; Wang et al., 2020). Furthermore, several herbal teas are considered significant dietary contributors to glycemic control by inhibiting PPGA with different mechanisms. There are studies showing that chamomile tea, which is mostly used as a single ingredient in complementary medicine, is one of them (Kato et al., 2008; Prasanna et al., 2016; Rafraf et al., 2015; Zemestani et al., 2016). However, underlying mechanism of action is yet to be elucidated. Particularly, literature about α-glucosidase inhibitory activity of chamomile is very limited and conflicting (Cvetanović et al., 2019; Franco et al., 2020; Qasem et al., 2022; Villa-Rodriguez Mr et al., 2015).

This study aims to evaluate *M. chamomilla* samples collected from different localities of Diyarbakır/Türkiye in terms of chamazulene and α-glucosidase inhibitory potential. To the best of our knowledge, there are no studies conducted on the samples of the region in the current context.

## 2. Material and Methods

### 2.1. Plant material

Flowering tops of *Matricaria chamomilla* L. samples were collected in April-May 2023 from different localities of Diyarbakır/Türkiye by the authors Ramazan Tunç and Hasan Şahin. Depositing of the voucher specimens (Şekerciler 4433) and the botanical identifications were made by the author Fatoş Şekerciler Subaşı. Locality details are given in Table 1. The plant materials were air-dried in the shadow at room temperature. Grinding and hand shredding were used for the preparing of the extracts and essential oils, respectively.

Table 1. Localities of collected *Matricaria chamomilla* L. samples.

| Sample | Locality |
|---|---|
| M1 | Bismil/Diyarbakır, Esentepe – 37.853457, 40.676172 |
| M2 | Sur/Diyarbakır, Campus of Dicle University – 37.894309, 40.273442 |
| M3 | Sur/Diyarbakır, Güzelköy-Karaçalı roadsides, 37.924348, 40.302071 |
| M4 | Bismil/Diyarbakır, Başaklı roadsides – 37.812725, 40.456002 |
| M5 | Dicle/Diyarbakır, Dedeköy, village entrance roadsides – 38.303688, 40.308382 |
| M6 | Karacadağ/Diyarbakır, Bağlar – 37.786260, 39.957419 |

### 2.2. Chemicals and reagents

All commercially available chemicals, p-nitrophenol, α-D-glucopyranoside (PNPG, N1377)), α-glucosidase type I (E.C. 3.2.20, G5003), $Na_2HPO_4$ (106586), $NaH_2PO_4$ (04269), $NaN_3$ (S2002), acarbose (A8980), DMSO, methanol, petroleum ether, and ethyl acetate were Sigma–Aldrich/Merck branded. All other chemicals were of analytical grade. Ultra-pure water was obtained from Milli-Q Lab Water System.

### 2.3. Extraction

Plant materials were subjected to maceration with petroleum ether, ethyl acetate, and methanol separately (3x24h). Infusion extracts were prepared with drinking water by adding boiled water on the plant material and filtering after 10 minutes. All evaporation steps were conducted with a rotary evaporator (Buchi, R100, bath temperature 45 °C) until dryness. Essential oils were obtained by hydro-distillation using Clevenger Apparatus for 5 hours each. All extracts and essential oils were stored at 4-8 °C until further use.

### 2.4. Thin layer chromatography (TLC)

Qualitative analysis for chamazulene content of the essential oils was conducted by TLC according to the 10$^{th}$ edition of European Pharmacopoeia (Matricariae aetheroleum) (Council of Europe, 2019). TLC silica gel plate (Merck, $60F_{254}$) and ethyl acetate-toluene (5:95, V/V) mixture were used as stationary and mobile phases, respectively. Plate was examined in daylight after developing towards a blue zone at the top. Then, freshly prepared anisaldehyde solution consisting of 0.5 mL anisaldehyde, 10 mL glacial acetic acid, 85 mL methanol, and 5 ml sulfuric acid was sprayed to the plate and heated at 100-105°C for about 7 minutes. Plate was examined immediately for reddish-violet zones at the top.

### 2.5. α-Glucosidase inhibitory assay

A previously described method was used with minor changes for α-glucosidase inhibitory assay (Schmidt et al., 2012). In brief, 10 µL of the extracts and essential oils dissolved in DMSO were added to the wells along with 90 µL of phosphate buffer (pH 7.5) which was prepared by

using $Na_2HPO_4$, $NaH_2PO_4$, ultra-pure water (Milli-Q), and $NaN_3$ (0.02%). 80 µL of enzyme (α-glucosidase Type I, 0.05 U/mL) solution was added and the mixture was incubated at 28°C for 10 minutes. Then, 20 µL of the substrate (p-nitrophenol, α-D-glucopyranoside, 1.0 mM) was added to each well. The blank wells consisted of the same mixture with buffer (DMSO 10%) instead of sample solutions. BioTek Power Wave XS microplate photometer was used for incubations and absorbance measurements at 405 nm. Photometer was set to read the absorbances every 40 seconds for 35 minutes to obtain an absorbance/time graph. Slopes of the graphs were used to eliminate the potential influence of the colored samples on absorbance. Following formula was used to calculate the percentage inhibitions.

$$\text{Inhibition \%} = (\text{Slope}_{\text{blank}} - \text{Slope}_{\text{sample}}) / \text{Slope}_{\text{blank}} * 100$$

Acarbose was used as positive control. Each measurement was repeated three times. Statistical comparisons were performed with Student's t-test ($p < 0.05$) and the results were expressed as mean ± standard deviation.

**3. Results and Discussion**

Table 2 shows the yields of extraction processes. The highest yields for every plant sample were observed in water and methanol extracts respectively, among the solvents used. The least amounts of extracts were obtained with petroleum ether. The highest yield for essential oils was determined in samples collected from M4 – Bismil. Samples of this district provided approximately 2.5 times higher amounts of essential oils than other efficient districts. The poorest samples for essential oil belonged to M1 – Bismil and M5 – Dicle districts. Chamomile flowers should yield minimum 4 mL/kg (dried drug) according to the European Pharmacopoeia 10th edition (Council of Europe, 2019). The density of the oil was reported as 0.925 g/mL (Herrera et al., 2022). Thus, dried *M. chamomilla* flowers should contain approximately 0.37 % weight EO/weight dried plant sample essential oil. Current results revealed that M4 – Bismil and M6 – Karacadağ samples met this criterion. However, M1 – Bismil, M5 – Dicle, M2 – Sur, and M3 – Sur samples did not meet the criterion while the latter two had very close yields.

Table 2. Yields of *Matricaria chamomilla* L. extracts and essential oils (%).

| | Yield % | | | | |
|---|---|---|---|---|---|
| Plant sample | PE | EA | Me | INF | EO |
| M1 | 3.20 | 3.35 | 12.06 | 17.94 | 0.18 |
| M2 | 2.04 | 3.71 | 17.01 | 24.30 | 0.34 |
| M3 | 3.36 | 3.28 | 12.95 | 22.23 | 0.31 |
| M4 | 2.63 | 6.29 | 21.94 | 24.84 | 0.82 |
| M5 | 1.42 | 1.88 | 10.10 | 14.64 | 0.17 |
| M6 | 1.65 | 2.78 | 12.12 | 22.33 | 0.38 |

All yields % were calculated in weight extract / weight dried plant sample. PE: Petroleum ether, EA: Ethyl acetate, Me: Methanol, INF: Infusion, EO: Essential oil

Essential oils obtained from all samples were yellowish orange colored instead of intense blue. Unfortunately, the colors and TLC analysis of the essential oils show that none of these samples contain chamazulene, and so no proazulenic sesquiterpene lactone, matricin (Fig. 1). There are several studies conducted on *M. chamomilla* samples originated from Anatolia reporting no chamazulene content. Nevertheless, it is recorded that some natural samples and samples grown in Türkiye with imported seeds yield blue essential oil (Baytop, 1999; Mericli, 1990; Özdemir et al., 2021). Using chamomile to treat inflammatory based diseases is a well-known and well-established traditional fact. The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) approves the use of chamomile orally and topically to manage inflammatory disorders of gastrointestinal tract and various mucosal membranes such as mouth. Particularly, oral inflammatory diseases such as mucositis and stomatitis occurring during cancer chemotherapy have become an important application area of chamomile as an integrative medicine agent. Managing the pain and inflammation in cancer patients is crucial for the continuation of the treatment. Furthermore, there are commercially available preparations of chamomile, such as mouthwashes, standardized with chamazulene content for palliative care of cancer patients. Current literature provides several *in-vitro*, *in-vivo*, and clinical studies attributing the anti-inflammatory activity of chamomile to guaianolide structured sesquiterpene lactones such as matricin and its degradation product chamazulene. The increase in number of such reports raises questions about the medicinal use of chamazulene-free chamomile. This is one of the numerous proofs that herbal materials to be used for medicinal purposes must be of pharmaceutical quality. However, it should be noted that there are several reports revealing high anti-inflammatory potential of flavonoids, non-lactone sesquiterpenoids, and essential oil of chamomile too. Particularly, potentials of oxidized bisabolene derivatives such as α-bisabolol, bisabololoxid A or bisabolonoxid stand out. Even more, polyketides of chamomile such as dicycloether derivatives reported as possible contributors to the anti-inflammatory activity (Akbaş et al., 2023; Capuzzo et al., 2014; El Joumaa & Borjac, 2022; Flemming et al., 2015; Maurya et al., 2014; Tomić et al., 2014). In this context, it can be deduced that studied samples of Diyarbakır with other sesquiterpene-lactone-free chamomiles might provide less anti-inflammatory potency than chamazulene containing chamomile but are not completely dysfunctional in phytotherapy. Furthermore, high essential oil yield of the sample M4 points out that cultivation of the plant with pharmaceutical grade chamomile seeds might be considered in Bismil district which is already a very important agricultural area of Diyarbakır.

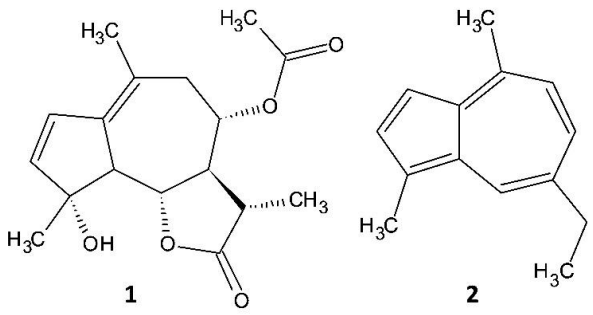


Figure 1. Structures of matricin (1) and chamazulene (2).

Table 3 shows the results obtained from *in-vitro* hypoglycemic activity studies of *M. chamomilla* extracts. PE, EA, Me, and INF extracts which were prepared in increasing polarity manner with petroleum ether, ethyl acetate, methanol, and water respectively showed the same pattern in α-glucosidase inhibitory potential. All samples showed an increase in the activity from PE to EA and then a decrease from EA to INF (Fig. 2). Samples collected from M1, M2, and M3 districts have better antidiabetic potentials in all extracts. However, EA extracts of these samples have the highest inhibitory activity and the potencies are comparable to that of standard acarbose. Further studies to find potent α-glucosidase inhibitors might be considered on these extracts. All essential oils revealed better potentials for the inhibition than that of extracts, considering the concentrations. However, essential oil of M2 district showed the best α-glucosidase inhibitory potential (92.22 % at 0.5 mg/mL) compared to the other essential oils and acarbose (97.59 % at 2 mg/mL).

Table 3. α-Glucosidase inhibitory activity of *Matricaria chamomilla* L. extracts.

| Sample | Inhibition % ± SD | Sample | Inhibition % ± SD |
|---|---|---|---|
| M1PE | 88.31 ± 3.58 | M4PE | 15.27 ± 1.81 |
| M1EA | 95.34 ± 3.05 | M4EA | 38.32 ± 11.86 |
| M1Me | 63.50 ± 3.14 | M4Me | 22.89 ± 0.71 |
| M1INF | 50.22 ± 2.61 | M4INF | 10.77 ± 0.67 |
| M1EO | 60.16 ± 7.67 | M4EO | 79.76 ± 1.48 |
| M2PE | 49.33 ± 0.63 | M5PE | 2.03 ± 0.98 |
| M2EA | 95.27 ± 1.89 | M5EA | 82.34 ± 1.95 |
| M2Me | 67.72 ± 0.37 | M5Me | 55.92 ± 0.96 |
| M2INF | 55.92 ± 1.18 | M5INF | 5.84 ± 1.67 |
| M2EO | 92.22 ± 5.81 | M5EO | 64.74 ± 6.07 |
| M3PE | 81.51 ± 4.95 | M6PE | 10.33 ± 4.24 |
| M3EA | 98.05 ± 2.57 | M6EA | 75.74 ± 2.39 |
| M3Me | 65.98 ± 0.87 | M6Me | 65.05 ± 3.20 |
| M3INF | 70.89 ± 0.86 | M6INF | 45.60 ± 1.21 |
| M3EO | 82.81 ± 11.81 | M6EO | 89.65 ± 13.42 |
| Acarbose | 97.59 ± 2.96 | | |

PE: Petroleum ether, EA: Ethyl acetate, Me: Methanol, INF: Infusion with water, EO: Essential oil. Concentrations of all extracts and standard acarbose: 2 mg/mL, essential oils: 0.5 mg/mL. All values are presented as mean ± SD (n=3). Statistical comparisons were performed with Student's t-test ($p < 0.05$).

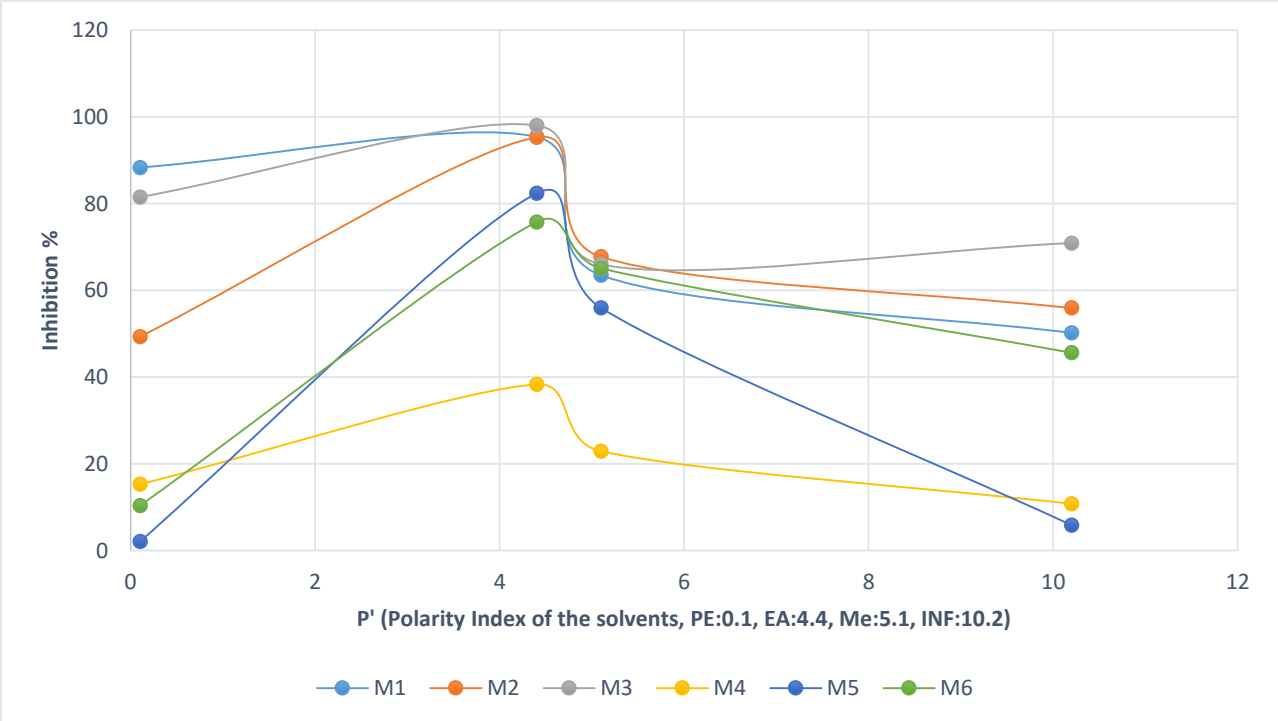


Figure 2. Changes in α-glucosidase inhibition potency of the extracts with the solvent polarity. PE: Petroleum ether, EA: Ethyl acetate, Me: Methanol, INF: Infusion with water.

Around the world, countless cups of chamomile tea are traditionally consumed every day for the prevention, care or treatment of many disorders including diabetes (El Mihyaoui et al., 2022). There are several *in-vitro* and *in-vivo* studies reporting antihyperglycemic, antioxidant, and antihyperlipidemic activities of chamomile (Cemek et al., 2008; Prasanna et al., 2016). Furthermore, protective and beneficial effects of chamomile on diabetic complications and glycemic control have been proposed by several studies (Hajizadeh-Sharafabad et al., 2020; Kato et al., 2008; Rafraf et al., 2015; Zemestani et al., 2016). These studies include several different methods such as sucrose loading test, measuring of hepatic glycogen levels, inhibition of aldose reductase ($ALR_2$) enzyme, and various animal and clinical trials. However, the mechanism of action of chamomile's antidiabetic activity is still to be elucidated. It has been reported that the antidiabetic effect of chamomile may be due to the prevention of excessive postprandial glucose concentration by inhibition of salivary human amylase but not intestinal maltase which is a type of α-glucosidase (Villa-Rodriguez Mr et al., 2015). However, current results revealed that α-glucosidase inhibition might be a significant contributor to the antidiabetic effects of chamomile. Another study conducted on chamazulene containing essential oil of chamomile reported potent α-glucosidase inhibition comparable to that of acarbose, in accordance with the current results (Qasem et al., 2022). Tea prepared by infusion is the most common way of using chamomile. However, current results revealed lower α-glucosidase inhibitory activity for infusions compared to the extracts prepared with organic solvents. Same pattern was determined for all six different samples. The results suggest that using chamomile phytotherapeutics prepared with the ethyl acetate extracts might be favorable for preventing postprandial hyperglycaemia in diabetic patients instead of drinking infusions. However, further studies are needed to provide a solid basis for a safe and accurate use of chamomile with complementary medicinal purposes for diabetics.

In conclusion, medicinal use of chamomile against inflammatory diseases with the samples collected from Diyarbakır/Türkiye might provide less antiphlogistic potential due to lack of sesquiterpene lactones and chamazulene. Samples collected from the Bismil district have an essential oil yield of approximately 2.5 times the minimum standard specified in the European Pharmacopoeia. Therefore, the region might be considered for medicinal chamomile culture. Ethyl acetate extracts and essential oils of all samples except M4-Bismil showed high antidiabetic potential and should be considered in further studies for novel α-glucosidase inhibitors. This inhibition might be one of the significant contributors to the underlying mechanism of action of chamomile's antidiabetic effects.

**Ethics committee approval:** Ethics committee approval is not required for this study.

**Conflict of interest:** The authors declare that there is no conflict of interest.

**Author Contributions:** Conception – H.Ş.; Design – H.Ş.; Materials – H.Ş., R.T., F.Ş.S.; Data Collection and Processing – H.Ş., R.T., F.Ş.S.; Analysis Interpretation – H.Ş.; Literature Review – H.Ş., R.T., F.Ş.S.; Writing – H.Ş.; Critical Review – H.Ş., R.T., F.Ş.S.

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