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EVALUATION OF HERBAL TOPICAL APPLICATIONS WITH *MATRICARIA RECUTITA*

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MASTERS THESIS

DEPARTMENT OF PYHTOTHERAPY

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STATEMENT (DECLARATION)

I hereby declare that this thesis is exclusively the result of my personal work, from its conception to its completion. I have scrupulously respected all the ethical rules which are essential for such a study. Any statement or comment borrowed is mentioned as such and rigorously referred. Consequently, this study followed all the approaches aimed at respecting the rights of participants during fieldwork, and respecting patent rights and copyright throughout its drafting.

Jean Christophe FOGANG VOUGMO

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At the time of presenting this work, I would like to address my thanks
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To the whole FOGANG family.

IN MOMORIAM

Of my lovely fathers

FOGANG Jean De Dieu

TEMOGOU YOUDA

Martin

May your souls rest in peace.

ÖZET

Öğrencinin Adı-Soyadı: Jean Christophe FOGANG VOUGMO

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Mayıs papatyası olarak da bilinen *Matricaria recutita* L., Astaraceae ailesinin bir üyesidir ve Avrupa ve Batı Asya'da büyük ölçüde kültürü yapılmaktadır. Papatya, dünyada en çok kullanılan ve üzerinde iyi çalışılmış bitkilerden biridir. Çiçek kısmıları anti-inflamatuar, antibakteriyel ve antifungal özellikleri içeren çeşitli farmakolojik aktivitelere sahip olduğu bulunmuştur;. Bu çalışmanın amacı, kozmetik ve ilaç endüstrisinde değerli olan uçucu yağ bileşenlerini analiz etmek ve *Matricaria recutita'nın*uçucu yağını içeren bir bitkisel oral jel hazırlamak ve değerlendirmektir. Papatya özü flavonoidler, kamazulen, α-bisabolol, bisabolol oxid A ve B terpenler gibi bileşiklere sahiptir ve flavonoidler bu farmakolojik aktivitelerden sorumlu birçok maddeden bazılarıdır. Papatya esansiyel yağı *Matricaria recutita*'nın çiçek kısımlarından ekstrakte edildi ve bileşenlerin analizi Gaz Kromatografi Kütle Spektrometrisi ile yapıldı. Uçucu yağ ekstraktının fizikokimyasal özelliklerine bağlı olarak en uygun jel bazına karar vermek için ön formülasyon çalışmaları yapılmıştır. Carbopol 940P kullanılarak dört plasebo jel formülasyonu yapıldı ve Hidroksipropilmetil selüloz sırasıyla %0.5 veya %1 ve %2 veya %2.5 (a/a) konsantrasyonlarında kullanıldı. Tüm plasebo formülasyonlarının değerlendirilmesi, organoleptik özellikler (renk, koku), pH ve viskozite gibi farklı parametrelerin analizi ile yapıldı. a-bisabolen oksit A ve chamazulene gibi bileşikler tespit edildi. %1 Carbopol 940P ve %2.5 Hidroksipropilmetil selüloz içeren plasebo formülasyonları, istenen aralıkta pH ile iyi bir tutarlılık, görünüm ve hiçbir ayrılma göstermedi. Her iki jel de kesmeyle inceltme yeteneği gösterdi; kayma gerilmesi arttıkça viskozite azalmıştır. Ön formülasyon çalışmalarından elde edilen sonuçlar, yukarıda bahsedilen her iki plasebo formülasyonunun, anti-enflamatuar ve anti-bakteriyel aktiviteleri için ayrıca değerlendirilecek olan bir bitkisel topikal jel üretmek için uygun olduğunu göstermektedir. Bir sonraki araştırma aşamasının, papatya uçucu yağı içeren jellerin anti-inflamatuar ve anti-bakteriyel aktivitelerinin araştırılmasıdır.

Anahtar Kelimeler: *Matricaria recutita*, kimyasal bileşen, ön formülasyon, oral jel, antiinflamatuar

ABSTRACT

Name of the Student: Jean Christophe FOGANG VOUGMO

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Chamomile, by its scientific name *Matricaria recutita* L. is a member of Asteraceae family and it grow vastly in Europe and western Asia. It is among the well-studied and widely used herbs in the world. Flowers, which are the most used part of the plant has been found to have several pharmacological properties including anti-inflammatory, antibacterial, antifungal activities. This study aimed to analyse *Matricaria recutita* L. essential oil constituents, which are valuable in cosmetics and pharmaceutical industries and prepare and evaluate a herbal oral gel which contains essential oil extract of *Matricaria recutita* L. Chamomile extract are rich in differents compounds such as chamazulene, bisabolol oxides A and B, alpha bisabolol, flavonoids and terpens, Those constituents are responsible for the pharmacological properties. Chamomile essential oil was extracted from aerial parts of *Matricaria recutita* L. and the analysis of the constituents was performed by Gas Chromotography Mass Spectrometry. Preformulation studies was carried out to decide the most suitable gel base depending on the physichochemical properties of the essential oil extract. Four placebo gel formualtions were made using Carbopol 940P and Hydroxypropylmethyl cellulose were used in concentrations 0.5% or 1% and 2% or 2.5% (w/w) respectively. The evaluation of all placebo formulations was done by the analysis of different parameteres such as organoleptic properties (colour, odour), pH, and viscosity. Compounds such as α-bisabolene oxide A and chamazulene was detected. Placebo formulations with 1% Carbopol 940P and 2.5% Hydroxypropylmethyl cellulose showed good consistency, appearance, and no separation with the pH within the desired range. Both gels showed shear thining ability; as the shear stress increased, the viscosity decreased. Results from the preformulation studies suggest that both placebo formulations mentioned above are suitable to produce a herbal topical gel, which will be further evaluated for its anti-inflammatory and antibacterial activities. It is anticipated that the next research stage will address its anti-inflammatory and antibacterial activities produced by the gels containing chamomile essential oil.

Keywords: *Matricaria recutita* L., chemical constituent, pre formulation, oral gel, anti-inflammatory.

TABLE OF CONTENT

LIST OF TABLE

LIST OF FIGURES

ABBREVIATION AND SYMBOLS

BC : Before Christ

eV : electron-Volt

FDI : World Dental Federation

FID : Flame Ionization Detector

GC : Gas Chromatography

GC-MS : Gas Chromatography-Mass Spectrometry

GDB : Global Burden of Disease

HPMC : HydroxyPropyl MethylCellulose

LRI : Linear Retention Index

MIC: Minimum Bactericidal Concentration

MIC: Minimum Bnhibitory Concentration

MS : Mass Spectrometry

PMS : Pre-Menstrual Syndrom

RRI : Relative Retention Indices

tr : Trace

UHC : Universal Health Coverage

WHO : World Health Organization

1. INTRODUCTION

1.1. Herbal Formulation for Topical

Several plants have shown their effectiveness in topical use. They come in single or combined formulations.

Refering on Iranian traditional medicine, a wound healing polyherbal topical formulation, using leaves aqueous extracts of *Malva sylvestris* and *Solanum nigrum*, and petals oily extract of *Rosa damascena*, was prepared and shows its effectiveness (Fahimi et al. 2016). Another formulation using a combination of *Cardiospernum halicacabun* and *Vitex negundo* extracts displayed significant anti-arthritic activity (Aiyalu, Govindarjan, and Ramasamy 2016). Kuchekar and Bhise development an antipsoriatic herbal gelcream using Simugel NS (2% w/v), Sepicide HB (2% w/v) and *Commiphora myrrha* oil which gave better anti-inflammatory gelcream with good consistency and stability (Kuchekar and Bhise 2012). Madadi et al. also made an herbal oil in water cream containing 2,5% of each hydroalcoholic extract of *Rheum palmatum* and *Rosa canina* that show acceptable pharmaceutical behavior as a nutural formulation to be further study in the field of hyperpigmentation (Madadi et al. 2017). By combining both ripe and unripe fruit pulp of *Aegle marmelos*, leaves of *Nyctanthes arbor-tristis*, terminal meristem of *Musa paradisica* flower, Kalyana Sundaram et al. prepared a poly herbal formulation that can potentialy be used as an anti-aging agent in skin creams as well as an anti-proliferation medicine against cancer cells (Kalyana Sundaram et al. 2018). Aqueous lyophylized leaves extract of Hippophae rhamnoides L. combine with that of Aloes vera L. and the ethanol rhyzome extract of Curcuma longa L., lead to a polyherbal formulation that possesses significant wound healing property in both normal as well as chronic diabetic wounds (A. Gupta et al. 2008).

1.2. *Matricaria recutita L.* in topical Appllications

Matricaria recutita L. (Asteraceae), which is known as chamomile has been found to demonstrate several therapeutic effects. Its anti-inflammatory properties have been widely described in literature (Srivastava, Shankar, and Gupta 2010). Also, other effects such as sedative, antiallergic, antimicrobial, antihyperglycemic and antispasmodic, have been attributed to chamomile thereby justifying the recognized

use as medicinal herb (Haghi et al. 2014). In addition *Matricaria recutita* has been used to ease rheumatic and arthritis pains by different traditional medicines (Zargaran et al. 2018). Many different components such as sesquiterpens, coumarins and flavonoids are found in Chamomile. Apigeninis is a flavonoid found in larger quantities in chamomile flowers and is responsible of the highlighted pharmacological properties (Khaki, Sahari, and Barzegar 2012). With the knowledge of the pharmacological properties of chamomile, the interest in the topical effect of chamomile spiked which led to several studies comprising of topical formulations such as gels, cream, ointments, lotions etc. containing ethanolic extracts or essential oil of chamomile to investigate its efficacy.

Another study investigated the efficacy and safety of chamomile oil in knee osteoarthritis. Chamomile oil significantly reduced patients pains. It was concluded that chamomile oil was beneficial on the use of analgesic by patients with knee osteoarthritis. In addition, chamomile oil showed beneficial effects on stiffness and physical activity of the patients (Shoara et al. 2015). The description of the studies above affirms that chamomile has the potential to be an effective anti-inflammatory herb. It is therefore imperative to develop topical formulations alongside comparative clinical studies testing to promote the use and the reproducibility of topical pharmaceutical preparations containing chamomile.

Despite the many benefits that can be found in the use of chamomile, it is however necessary to note certain rather questioning aspects. *Matricaria recutita* L. (principally, unwrapped chamomile) is a potential vector agent for *Clostridium botulinum* that can cause botulism in children (Bianco et al. 2008). Also, some studies shows that in certains cases, chamomile does not respond to certain properties attributed to it. For example, a clinical trial was conducted aiming to evaluate the effectiveness of a chamomile cream formulation containing 10 % of ethanolic extract and compared with a placebo cosmetic cream. 44 individuals with eczema like lesions were used as subjects and it was found that there was a high response rate both in those who received chamomile cream as well as in those who received placebo cream, with no statistically significant difference between them. (Shimelis et al. 2012).

Since chamazulene, farnesene and alpha bisabolol inhibit CYP2D6, there is a theoretical risk of interaction between all blue chamomile oil and drugs metabolized

by this enzyme. The α-bisabolol/(E)-□-farnesene may also inhibit CYP1A2, CYP2C9 or CYP3A4. The α-bisabolol oxide A may inhibit CYP1A2 (Tisserand and Young 2013).

The aim of this study analyse essential oil constituents, which are valuable in cosmetics and pharmaceutical industries and design an herbal formulation.

1.3. *Matricaria recutita* L. (Asteraceae)

1.3.1. Taxonomy, Origin and habitat

According to Arctos database, *Matricaria recutita* L. is classifiyed as follow:

- Kingdom of Plantae;
- Phylum of Tracheophyta;
- Class of Magnoliopsida;
- Order of Asterales;
- Familly of Asteraceae;
- Genus *Matricaria*;
- Specy *Matricaria recutita* (Arctos database 2021).

Belonging to the Asteraceae family, chamomile by its scientific name *Matricaria recutita* L. is indigeneously a Northern European plant that grows wild in Central European countries. It is mostly abundant in Eastern Europe and it is also found in Western Asia, in the Mediterranean region of Northern Africa and in the United States. It is thus cultivated in many countries (Franke and Schilcher 2005). Important quantities are also grown in Spain Turkey, Egypt and Argentina (Heinrich 2012), as well as Germany, Russia, Hungary, Brazil, France and Yugoslavia (Ompal Singh et al. 2011). Since it was introduce in India during the mughal period, it is grown in some regions such as Punjab, Pradesh, Uttar, Maharashtra, Kashmir and Jammu. The plant can also be found in other parts of Asia, North and South America, Australia and New Zealand. In Hungary, the plant is source of income to poor inhabitants and even grows in poor soils. This country export floers to Germany for oil distillation (Ompal Singh et al. 2011). Chamomile is one of the important medicinal herb used in these countries.

1.3.2. Morphology

The german chamomile otherwise hungarian chamomile flowers are devrived from *Matricaria recutita* which have many synonyms as *Chamomilla recutita, Matricaria chamomilla*. Those flowers with a pleasant aromatic odour, have a heads diameters of approximately 10 mm and are composed of many florets with are either tongue or tubular-shaped respectively called ligulate florets or disk florets. Distinct characteristics of true chamomile are the presence of a hollow receptacle and the abscence of small leaf-like structures called stipules, that are common with the non medicinal members of the the Matricaria genus (Heinrich 2012).

1.3.3. Botany

The true chamomile is an annual plant that grows 10 to 80 cm high. It prefers sandy to loamy soils and mostly sour and fresh places. It has a thin spindle-shaped roots that only penetrate flatty into the soil. The bare stem, round and vertical, vefry often strongly branched, is filled with pith. The leaves show an alternate arrangement and are double to triple pinnatipartite with narrow linear spiny pointed sections less than 0,5 mm wide. With a diameter between 10 and 30 mm, the flower heads are separated, stalked and heterogamous. The semi-spherical involucre bears 26 to 48 involucral leaves arranged in three rows. These leaves are ovoïd to lanceolate upside down, green with a narrow brownish membranous rim. Golden yellow in color, the five-teeth florets are 1.5 to 2.5 mm long and always end in a glandular tube. The flowering of the plant is done in a concentric way and from botton to top. Varying between 11 and 27, the white, recurved ligulate florets are 6 to 11 mm long and 3.5 mm widem longer than the involucre. The filamentous style shows two stigmata. The pollen has on its surface short prickles and three hila. The receptacle measures 6 to 8 mm wide, initially flat and conical, then conical, and hollow which is a very distinctive character and without a palea. Yellowish brown to brown, the fruit is an achene of 0.8 to 1.3 mm long about 0.3 mm wide. It is slighly pressed and curved in the shape of o horn, tapered at the base, truncated obliquely at the top, with four to five ribs on the concave underside. On the ribs small mucous glands are found, rounded on the back, ribless, poorly punctured with glands on the outside, humid and mucous. The pappus is missing or can be traced as a barely developed rim. The diploid forms fo one thousand grain

weight 0.02 to 0.06 grams while tetraploid forms weight 0.04 to 0.12 grams (Franke and Schilcher 2005) (see figure 2).

Plants belonging to the genera *Anthemis* and *Matricaria* are quite often confused with true chamomile. *Anthemis coluta* L deserves more attention in terms of confusion with *Matricaria recutita*. The following characters make it possible to make the difference between certain species and *Matricaria recutita*. *A. coluta* has bristle-like paleae a receptacle with marrow and a revolting odour. *A. arvensis L.* and *A. austriaca* Jacq. have prickly pointed paleae and a filled receptacle. However, both species are almost odorless, as well as *Matricaria maritima* L. and *Matricaria perforata* Mérat. These species have a filled receptacle but no paleae. *Chamomilla suaveolens* (Pursh) Rydb with its synonyms *Matricaria discoidea* DC and *Matricaria matricarioides* [Less.] Porter, has a typical true chamomile odor, but do not has ligulate flowers and can growth in a compact maner (Franke and Schilcher 2005).

Figure 1. Scheme of *Matricaria recutita* L.

Figure 2. Dried flower of *Matricaria recutita* L.

Figure 3. Fresh flowers

Figure 4. Stem and leaves

1.3.4. Drug name

In most formularies and reference books, *Matricaria chamomilla* L. is regarded as the correct species name. Howerver, according to the international Rules of Botanical Nomenclature, *Chamomilla recutita* (L.) Raushert is the legitimate name for this specy (World Health Organization 1999). Despite this legitime name in WHO monographs on selected plants, for Franke and Schilcher, the best-known botanical name for true chamomile, also used in the pharmacopoeias, is *Matricaria recutita* L. (syn. *Matricaria chamimilla* L., *Chamomilla recutita* (L.) Rauschert) (Franke and Schilcher 2005).

1.3.5. Pharmacological properties

Several pharmacological effects have been demonstrated on *Matricaria recutita* L. Table 1 shows its biological activities.

Table 1. Biological activities attributed to Matricaria recutita L.

Activity	**Active compounds**	**Dosages**	**References**
Analgesic	Matricine and alpha-bisabolol chamazulene apigenin	4.48 ± 0.01 µl/ml of chamazulen and 0.233 mg/g of apigenin	(Khare C.P. 2007; Zargaran et al. 2018)
Antiallergic	Ethyl acetate fraction of the ethanol extract of hot water extraction residue	Diet containing 5.09% of ethanol extract of hot water extract : 61.5% inhibition of pruritis	(Y. Kobayashi et al. 2003; Yoshinori Kobayashi, Takahashi, and Ogino 2005)
Anticancer	Essential oil	5, 50 and 500 mg/kg Dose-dependent effect	(Huang et al. 2015; Hernández-Ceruelos, Madrigal-Bujaidar, and de la Cruz 2002)
Antidiarrheal	Aqueous methanolic extract decoction extract s	150 and 300 mg/kg 25, 50 and 100 mg/kg Dose-dependent effect	(Mehmood et al. 2015; Sebai et al. 2014)

Antidepressive	Tea (infusion)	2 g of dried flowers in 300 ml	(Chang and Chen 2016)
Antigenotoxic	Essential oil	5 mg/kg (47.5% inhibition), 50 mg/kg (61,9% inhibition), 500 mg/kg (93.5% inhibition)	(Cosmetic Ingredient Review 2013)
Antihyperglycemic	Hydroalcoholic extract of the aerial part *chamomile* tea	20, 50, and 100 mg/kg. 200 mg/kg/d. Chamomile tea (3 g/150 mL hot water)	(Cemek et al. 2008; Weidner et al. 2013; Rafraf, Zemestani, and Asghari-Jafarabadi 2015; Khan et al. 2014)
Antiinflammatory	Flavonoid (apigenin) α-bisabolol chamazulene polysaccharides	Dose dependent 30 and 300 μg/mL	(Franke and Schilcher 2005; Batista et al. 2014; Miguel et al. 2015; 2015)
Anti-leech effect	Methanolic extract	600mg/ml	(Bahmani et al. 2012)
Antimicrobial	Essential oil	MIC : 0.011 to 4 µg/mL MBC : 0.5 to 8 µg/mL	(Nogueira, Diniz, and Lima 2008; Parlinska-Wojtan et al. 2016; Móricz et al. 2013; Göger et al. 2018)
Antipruritic	Ethyl acetate extract or essential oil	Ethyl acetate extract : 300 mg/kg	(Yoshinori Kobayashi, Takahashi, and Ogino 2005)
Antispasmodic	Aqueous-methanolic extract	150 and 300 mg/kg	(Mehmood et al. 2015)
Antiulcer	Aqueous-methanolic extract	150 and 300 mg/kg	(Mehmood et al. 2015)
Antioxydant	Bisabolol chamazulene aqueous extracts	25, 50, and 100 mg/kg	(Caleja et al. 2016; Mamalis et al. 2013; Agatonovic-Kustrin et

			al. 2015; Jabri et al. 2016)
Anti-oral mucositis	Kamillosan® Mouth rinse	370.5 mg/spray	(Mazokopakis et al. 2005; Carl and Emrich 1991)
Anxiolytic	hydro alcoholic extract	10, 30, and 50 mg/kg	(Amsterdam et al. 2009; Mahnnaz, Loghman, and Meysam 2014)
Arcaricadal property	Decoctions, infusions and macerates		(Macchioni et al. 2004)
Gastrointestinal disorders	In combination with myrrh and coffee Charcoal		(Mahady et al. 2005; Albrecht et al. 2015)
Hepatoprotective	Decoction		(Sebai et al. 2015)
Intracanal irrigant	hydroalcoholic extract		(Sadr Lahijani et al. 2006)
Lousicidal, ovicidal, repellent	Essential oil	Median lethal concentration LT50 : 18.67%	(Khater, Ramadan, and El-Madawy 2009)
Premenstrual syndrome	Ethanolic extract	capsule 100 mg	(F. Sharifi et al. 2014)
Rheumatic pain	aqueous extract in sesame oil	1.5 cc of chamomile oil/day for 3 weeks as ointment	(Shoara et al. 2015)
Uterotonic			(Shipochliev 1981)
Virucidal agent	Essential oil dilute in ethanol	Toxic concentration : 0.003%	(Koch et al. 2008)

Wound healing property	Ad-Muc® (pommade made with camomille extract)	100 mg equivalent to 0,30 mg of apigenina - 7 glucoside	(Martins et al. 2009; Motealleh et al. 2014)

1.3.6. Traditional usage

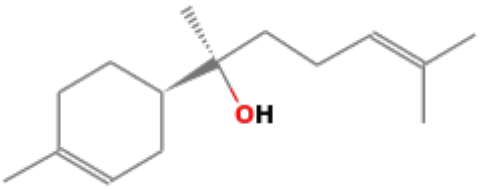
Included in the pharmacopoeia of 26 countries, *M. recutita* L. is believed by anglosaxons to be one of the nine sacred herbs given to humans by the Lord (Ompal Singh et al. 2011). It has been known as a medicinal plant for thousanda of years. It is used internally for spasmodic and inflammatory illnesses of the gastro-intestinal tract (Heinrich 2012), hay fever, menstrual disorders (V. Gupta et al. 2010). Leaves, flowers and stems of chamomile are used traditionally as antioxidant, analgesic, antiviral, antiseptic, antidiabetic, antiproliferative, antibacterial and many other health conditions. Its extracts has been used as a mild sedative to calm nerves and to reduce anxiety, to treat hysteria, nightmares, insomnia and other sleep problems (Mai Ramadan et al. 2006). Dried flowers of chamomile aer also used as herbal tea, baby massage oil, for promoting the gastric flow of secretion and for the treatment of cough and cold (Ompal Singh et al. 2011). Chamomile originated from Africa has a reputation to be used as herbal tea for the following actions, sedative, carminative, antiseptic, analgesic, antispasmodic, antidiarrheic and anti-inflammatory. It is also used in the treatment of gout, indigestion, insomnia and in pediatric practice for infantile convulsions, colic and teething pains (Iwu, 2015). In traditional Persian medicine, *Matricaria recutita* L. has been used as a treatment for enuresis of children (H. Sharifi et al. 2017). In many parts of Europe, South America and Mexico, chamomile tea is commonly used for children with colic and other disturbances, fever, insomnia and the restlessness and irritability commonly associate with teething. *Matricaria recutita* has been used for long by women in premenstrual syndrom and menstrual cramps. It has also been recommended as a nervine, for muscle cramps, headaches and to soothe indigestion and flatulent colic. Inhalation of steam from chamomile can be done for respiratory tract irritation. Its creams and ointments are applied to the skin to help soothe and heal burns and other skin irritations, wounds, diaper rash and sore nipples. The homeopathic tablets are given to babies for teething and fussiness (Bayati Zadeh, Moradi-Kor, and Kor 2013).

1.3.7. *Matricaria recutita* L. essential oil

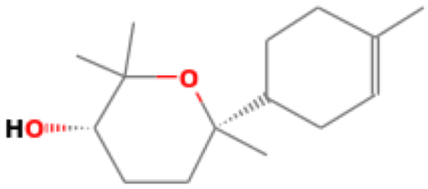
Flowers of *Matricaria recutita* L. produces a volatile oil with a pleasant smell, the sesquiterpene α-bisabolol composing up to 50%. The volatile oil content is about 2% of the dry weight of the flowers. Other volatile oil components include chamazulene, guiazuline, farnescene, α-bisabolol derivatives and matricine (Iwu, 2015).

At least four drug chemotypes can be distinguished according to the composition of the oil. The first chemotype is from European origin and characterized by the presence or absence of chamazulene. The second chemotype is the Portuguese and Spanish origin and is characterized by the presence of α- bisabolol. The third one is the African, Bulgarian and Turkish chemotype, characterized by α-bisaboloxide A. And finaly the fouth chemotype is the Argentina type which is characterized by the α- bisaboloxide B (Iwu, 2015). More than 120 constituents have been identified in chamomile flowers (Pino et al. 2002; Kazemi 2015; Sashidhara, Verma, and Ram 2006).

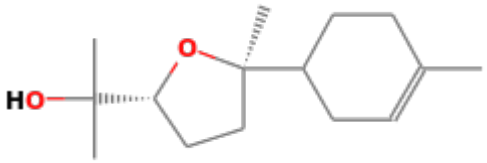
Sesquiterpene derivatives reoresent the vast majority of compounds in the essential oil of chamomile flowers, approximately 75 to 90% against only traces of monoterpenes. Polyynes can represent up to 20% of the composition of the oil, among other compounds such as (E)-β- farnescene (4.9 – 8,1%), terpene alcohol as farnesol, chamazulene (2.3 – 10.9%), α-bisabolol (4.8 – 11.3%), α-bisabolol oxides A (25.5 – 28.7%) and α-bisabolol oxides B (12,2 – 30.9%) (Ompal Singh et al. 2011).



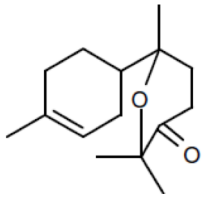
α-Bisabolol (NIST 2021b)



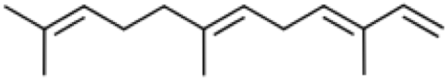
α-Bisabolol oxide A (NIST 2021a)



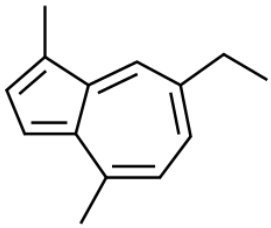
α-Bisabolol oxide B (NIST 2021a)



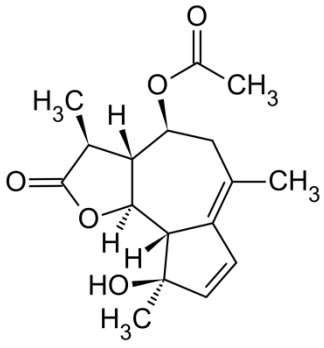
α-Bisabolone oxide A



α-farnescene (NIST 2021d)



Chamazulene (‘Chamazulene | C14H16 | ChemSpider’ 2021)



Matricine (‘Matricin’ 2021)

Figure 5. Some components of *Matricaria recutita* L. essential oil

1.3.8. Pharmacopeia- Quality properties of *Matricaria recutita* essential oil

European Pharmacopoeia (Ph. Eur 7.0) present Chamomile essential oil as a clear, instesely blue, viscous liquid with an intense characteristic odor (Acimovic et al. 2021). According to him, there are two types of essential oils, one rich in bisabolol oxides (between 29 – 81%) and the other rich in α-bisabolol (between 10-65%) (Acimovic et al. 2021).

European pharmacopoeia also recommends chamomile contains no less than 4 mL/kg of blue essential oil in crude dry flowers (V. Gupta et al. 2010).

1.3.9. Toxicity of *Matricaria recutita* essential oil

Several studies have been conducted to assess toxicity of *Matricaria recutita* L. essential oil. An oral and dermal dose of 5g/kg did not show any acute toxicity during 14 days of observations. Undiluted *Matricaria recutita* oil was shown to not irritate the eyes. The cutaneous irritation capacity of the essential oil of *Matricaria recutita* (4% in petrolatum) has been evaluated in 48 hours closed patch test involving human subjects. No skin irritation was observed (Opdyke 1974). The skin sensitization potential of *Matricaria recutita* oil was evaluated in the maximization test on 25 healthy volunteers aged 21 – 42. There was no eveodence of contact sensitization in any of the test subjects. But another study highlighted two of the 86 patients (3.4%) sensitive to *Matricaria recutita* oil (Cosmetic Ingredient Review 2013). Studies have been carried out to observe the effect of 3 doses of essential oil on the rate sister chromatid exchange (SCE) induced by a mutagenic agent, in particular daunorubicin, in the spermatogonia. *Matricaria recutita* oil was not genotoxic (Cosmetic Ingredient Review 2013).

2. MATERIALS AND METHODS

2.1. Sample collection

The flowers of *Matricaria recutita* L. were collected from Doganci April 28, 2021 by Assist. Prof. Dr. Azmi Hanoğlu, and then identified by Prof. Dr. Dudu Ozkum Yavuz. They were dryed in the shade in the laboratory for 30 days. The voucher specimen was kept at the Near East University Herbarium (NEUN6899).

2.2. Essential oil extraction

Matricaria recutita L. essential oil was obtained by hydrodistillation using a Clevenger apparatus. 100 g of dried flowers was introduce in a 2000 mL round bottom flask and 1000 mL of distilled water. The whole were distilled for 3 hours in order for flowers to be completly exhausted. At the end of distillation, due to its low density comparatively to water, a blue color essential oil were collected on the top of the distilled water. (See figure 6)

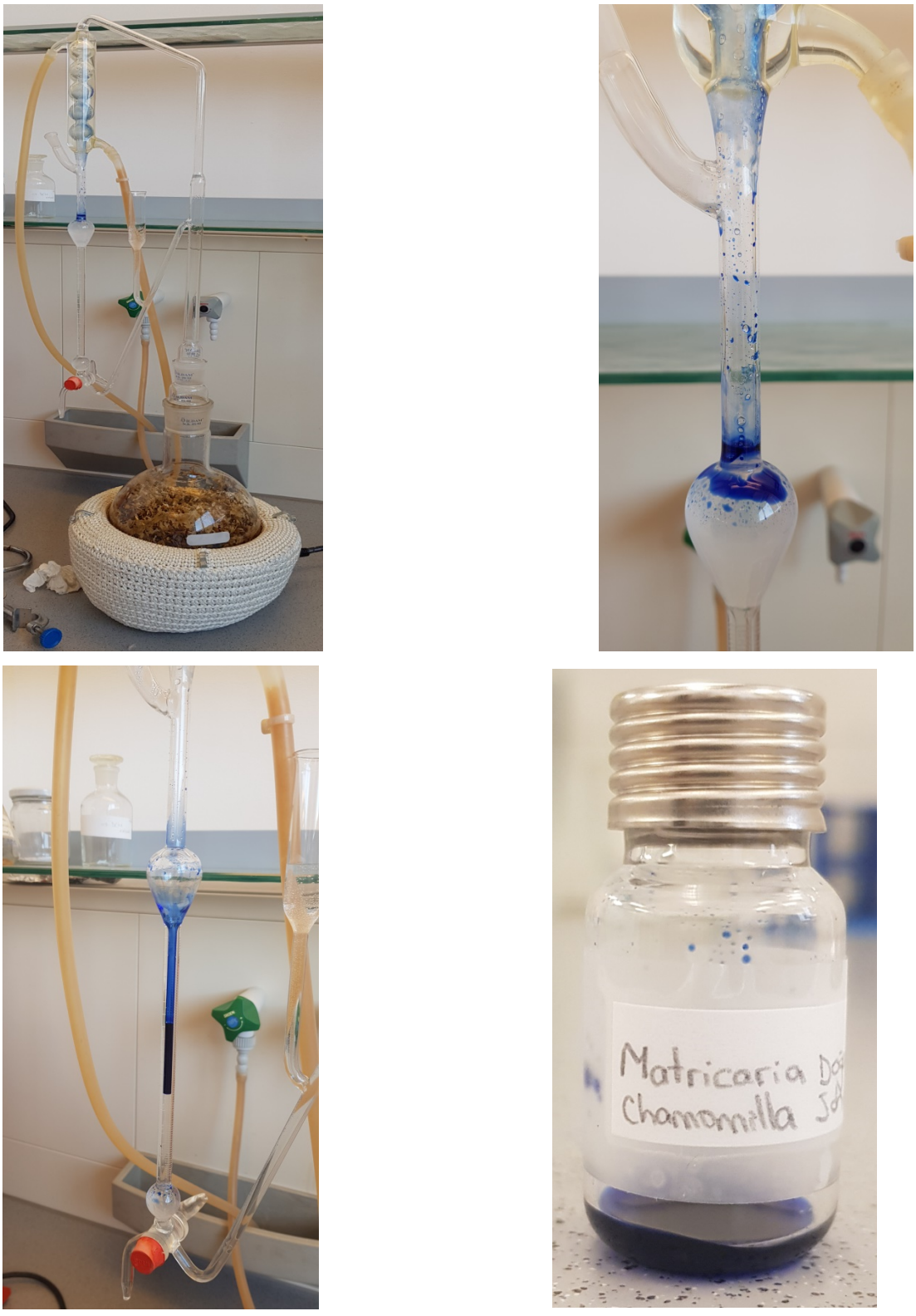


Figure 6. Extraction of *Matricaria recutita* L. essential oil

The collected oil wa stored at 4°C until the analysis and formulation.

2.3. Gas Chromatography (GC) and Gas Chromatography – Mass spectrometry (GC-MS) analysis

2.3.1. Gas Chromatography (GC)

GC analysis is carried out using an Agilent 7890B GC system. FID detector temperature is 300°C. to obtain the elution order with GC-MS, simultaneous auto-injection is done on a duplicate of the same column applying the same operational conditions. Relative percentage amounts of the separated compounds were calculated from FID chromatographs.

2.3.2. Gas Chromatography Mass Spectrometry (GC-MS) analysis

The GC-MS analysis is carried out using an Agilent 5977B GC-MSD. Innowax FSC column (60 mm x 0.25 mm, 0.25µ film thickness) was used with helium as carrier gas (0.8 mL/min). GC oven temperature was kept at 60°C for 10 min and programmed to 220°C at a rate of 4°C/min, and kept constant at 220°C for 10 min and then programmed to 240°C at a rate of 1°C/min. Split ratio was adjusted at 40:1. The injector temperature was set at 250°C. Mass spectra were recorded at 70eV. Mass range was from *m/z* 35 to 450.

2.3.3. Identification of constituents

This was carrued out by comparing the relative retention times of the essential oil constituents with those of authentic samples or by comparisons of their linear retention index (LRI) to series of n-alkanes. Computer matching against commercial (Wiley GC/MS library, NIST Chemistry WebBook) (McLafferty and Stauffer, 1989; Linstrom and Mallard, 2001) and in-house "Başer Library of Essential Oil Constituents" built up by genuine compounds of known oils, as well as MS literature dat used for the identification (Joulain and Koenig, 1998; ESO, 1999).

2.4. Formulation

Here the preparation of placebo gels has been made. Preformulation studies were carried out to decide the most suitable gel base depending on the physicochemical properties of the essential oil extract. pH measurement of the gels was carried out using

a digital pH meter. Viscosity of the gels was determined using Brookfield viscometer (DV-II+ Pro) at 20 rpm.

Preparation of Carbopol 940P gels

Methyl paraben (as preservative) was dissolved in 40°C purified water and then a specific amount of Carbopol 940P was mixed with it till homogenous using a magnetic stirrer with 1200 rpm for 30 minutes. A determined amount of glycerine was weighed and mixed well with the resulting gel to achieve a uniform gel. While monitoring the pH, triethanolamine was added to the gel for it to reach a pH of about 6.

Preparation of HPMC gels

Methyl paraben (as preservative) was dissolved in about one third of the formulation's water heated to 80°C and the a specific amount of HPMC was slowly added and mixed using magnetic stirrer in 1200 rpm. The remaining water was cooled and slowly added and mixed till a uniform gel was achieved. A determined amount of glycerine was weighed and mixed well with the resulting gel to achieve a uniform gel.

Table 2. Placebo gel formulations with different polymers (Carbomer 940, and HPMC)

Gel code	**Carbopol 940P (%)**	**HPMC (%)**	**Glycerin (%)**	**Methyl paraben (%)**	**Triethanolamine**	**Purified water (%)**
F1	0.5	-	10	0.1	q.s	q.s 100
F2	1	-	10	0.1	q.s	q.s 100
F3	-	2	10	0.1	-	q.s 100
F4	-	2.5	10	0.1	-	q.s 100

2.5. Evaluation of physical properties

Macroscopic tests and organoleptic properties

The formulations was studied 24 hours after preparation for macroscopic (lumps, color and transparency) and uniformity, gel texture and bubbles.

pH determination test

pH measurement of the gels was carried out using a digital pH meter. 1 gram of each formulation was dispersed in 10 mL purified water. pH was measured immediately after preparation, 24 hours and 48 hours after preparation and each time three repeats were done.

Viscosity test

Viscosity of the gels was determined using Brookfield viscometer (DV-II+ Pro) at 50 and 100 rpm. Each gel was poured into the container and the proper spindle (number 74) was attached. Then the viscosities were measured in 25°C and 50 – 100 rpm.

3. RESULTS AND DISCUSSION

From 100g of *Matricaria recutita* L. air dried flowers, 0.3 ml of essential oil was obtained. The extraction yield is 0.3% (v/w). This is quiet the same with the results obtained by Bucko and Salamon, who obtained 0.4% of essential oil in dryed flowers (Bucko and Salamon 2007). Nevertheless, extraction yield may depend on geographical area. Iranian chamomile gives 0.82% of essential oil (Kazemi 2015).

Table 3 shows the essential oil composition of *Matricaria recutita* L. found in Northern Cyprus. The major compounds are alpha-Bisabolone oxide A (74.4%), Chamazulene (12.0%), and alpha-Bisabolol oxide A (3.4%). Alpha-Bisabolone oxide A was found from the first time by Hölzl and Demuth while studying chamomile collected in Turkey (Franke and Schilcher 2005). So as we collected our plant in Northern Cyprus, and regarding its huge amount of Alpha-Bisabolone oxide A, we can affirm that Turkey and Cyprus share same *Matricaria recutita* L. species. However, some studies, including genetic studies, can confirm or refute this.

Table 3. Co;position of essential oil of *Matricaria recutita* L.

RRI	Compound	Percentage (**%**)
1032	a-Pinene	-
1035	a-Thujene	-
1048	2-Methyl-3-buten-2-ol	
1063	Ethyl 2-methyl butyrate	Tr
1076	Camphene	-
1093	*Hexanal*	
1118	b-Pinene	-
1146	d-2-Carene	-
1151	Propyl 2-methyl butyrate	Tr
1155	Butanol	Tr
1159	d-3-Carene	Tr
1203	Limonene	-

1213	1,8-Cineole	0.1
1244	Amyl furan	Tr
1255	g-Terpinene	Tr
1266	(*E*)-b-Ocimene	Tr
1280	*p*-Cymene	Tr
1290	2-Octanone	-
1299	2-Methylbutyl isovalerate	-
1348	6-Methyl-5-hepten-2-one	Tr
1358	Artemisiaketone	1.5
1403	Yomogi alcohol	0.2
1413	Rose furan	-
1435	Artemisyl acetate	0.1
1467	6-Methyl-5-hepten-2-ol	tr
1475	Acetic acid	-
1482	(*Z*)-3-Hexenyl-2-methyl butyrate	-
1483	Octyl acetate	-
1494	(Z)-3-Hexenyl isovalerate	0.1
1499	a-Campholene aldehyde	-
1480	(E)-2-hexenyl isovalerate	0.1
1510	Artemisia alcohol	0.3
1520	Formic acid	-
1532	Camphor	-
1541	Benzaldehyde	-
1553	Linalool	tr
1571	*Trans-p*-Menth-2-en-1-ol	-
1573	Unknown-MW:154	tr

1600	b-Elemene	tr
1590	Bornyl acetate	tr
1602	6-Methyl-3,5-heptadien-2-one	-
1612	b-Caryophyllene	tr
1611	Terpinen-4-ol	-
1617	Lavandulyl acetate	0.1
1625	4,4-Dimethyl but-2-enolide	-
1650	Ipsdienol	0.1
1662	(3*E*)-4,8-Dimethyl-3,8-nonadien-2-one	0.1
1668	(*Z*)-b-Farnesene	0.9
1670	*Trans*-Pinocarveol	-
1671	Acetophenone	-
1683	*trans*-Verbenol	-
1683	Lavandulol	0.1
1684	*trans*-Chrysanthemol	0.2
1706	a-Terpineol	tr
1719	Borneol	tr
1725	Verbenone	-
1726	Germacrene D	tr
1730	1,2-Dehydrosesquicineole	tr
1742	b-Selinene	tr
1748	Piperitone	-
1751	Carvone	-
1755	Bicyclogermacrene	-
1758	(*E,E*)-a-Farnesene	tr
1770	Isobornyl isovalerate	-

1804	Myrtenol	-
1845	*trans*-Carveol	-
1864	*p*-Cymen-8-ol	-
1868	(*E*)-Geranyl acetone	-
1882	*Cis*-Carveol	-
1902	Benzyl isovalerate	tr
1933	Neryl valerate	-
1945	1,5-Epoxy-salivial(4)14-ene	-
1946	Unknown-MW:220	-
1961	Dendrolasin	0.1
1970	6-Hydroxy-caryophyllene	0.1
1975	Unknown-MW:248	-
1981	Unknown-MW:220	tr
1988	2-Phenylethyl-2-methylbutyrate	0.1
2008	Caryophyllene oxide	tr
2020	Octyl octanoate	tr
2030	Methyl eugenol	-
2037	Salvial-4(14)-en-1-one	-
2040	1-Phenyl-penta-2,4-diyne	-
2050	(*E*)-Nerolidol	0.1
2067	Unknown-MW:178	tr
2095	Unknown-MW:218	tr
2128	Unknown	tr
2135	Unknown-MW:202	0.1
2148	Unknown	-
2071	Humulene epoxide-II	-

2090	Junenol	-
2098	Hedycaryol	-
2131	Hexahydrofarnesyl acetone	-
2144	Spathulenol	0.1
2148	Unknown-MW:236	0.1
2156	a-Bisabolol oxide B	1.3
2165	Unknown-MW:236	tr
2175	Nonanoic acid	-
2183	g-Decalactone	-
2180	Unknown	0.1
2187	T-Cadinol	0.3
2204	**a-Bisabolone oxide A**	**74.4**
2239	Carvacrol	0.6
2256	*Epi-a*-Bisabolol	0.3
2257	b-Eudesmol	0.1
2260	Unknown-MW:236	-
2265	Unknown	-
2265	Torilenol	-
2269	*trans*-a-Bergamotol	-
2288	Unknown-MW:222	tr
2292	b-Sinensal	tr
2298	Decanoic acid	0.1
2299	Unknown	tr
2300	Tricosane	0.1
2303	Limonene glycol	-
2307	Unknown	-

2316	Caryophylla-2(12),6(13)-dien-5b-ol	-
2324	Caryophylla-2(12),6(13)-dien-5a-ol	-
2330	13-Nor-7,8-epoxy-eremophil-1(10)-en-11-one	-
2350	Unknown	-
2357	t*rans*-Sobrerol	-
2366	Eudesma-4(15),7-dien-1-b-ol	-
2368	Hexyl cinnamate	-
2383	Unknown	-
2389	Caryophylla-2(12),6-dien-5a-ol	-
2392	Caryophylla-2(12),6-dien-5b-ol	-
2395	Unknown	-
2397	Unknown	-
2400	Tetracosane	0.1
2410	Unknown	-
2430	**Chamazulene**	**12.0**
2435	**a-Bisabolol oxide A**	**3.4**
2445	Benzoic acid	-
2473	Unknown	-
2500	Pentacosane	0.6
2503	Dodecanoic acid	-
2508	*trans*-2,6-Dimethyl-heptan-5-olide	-
2562	Sedanolide	-
2600	Hexacosane	-
2635	(Z)-Octadec-9-en-18-olide	0.1
2670	Tetradecanoic acid	0.2
2700	Heptacosane	0.1

2788	Unknown	-
2795	Unknown	-
2800	Octacosane	-
2822	Pentadecanoic acid	-
2931	Hexadecanoic acid	0.3
3000	Triacontane	-
	Total	**98.7**

RRI = Relative Retention Indices, calculated against n-alkanes

% calculated from FID data

Tr Trace (< 0.1%)

With a concentration of bisabolol oxides of 74.4%, our extracted *Matricaria recutita* L. essential oil is conform to European Pharmacopoeia (Ph. Eur 7.0) which recommend one type of *Matricaria recutita* L. essential oil should contain a level bisabolol oxides ranging between 29 and 81%. In fact, depending on the percentages of bisabolol oxides and alpha bisabolol, European pharmacopoeia differenciate two types of *Matricaria recutita* L. essential oil. The first type should contain a percentage of bisabolol oxides ranging between 29 – 81 %, and the second type should contain a percentage of alpha bisabolol ranging beatween 10 – 65 %. And both two types should contain a percentage of chamazulene superior or equal to 10%. With the respectives percentages of bisabolol oxides, alpha bisabolol and chamazulene of 74.4%, 5% and 12%, the extracted essential oil belong to type 1 regarding the European pharmacopoeia recommendations and it is suitable to be used in a formulation.

But our essential oil concentration (0.3%) did not match the Pharmacopoeia recommendation that says the oil concentration should not be less than 4 mL/kg (V. Gupta et al. 2010).

Placebo formulations with 1% Carbopol 940P and 2.5% HPMC showed good consistency, appearance, and no separation with the pH within the desired range. There is a high level of agreement that topical products should be acidified and have a pH between 4 and 6 (Lukić, Pantelić, and Savić 2021). Our preparations show all pH

higher than the recommendations. But since there are placebo gels, the pH will be adjusted once essential oil will be add to the formulations.

Both gels showed shear thinning ability; as the shear stress increased, the viscosity decreased.

There were no observable changes in the appearance of the gels, they kept their uniformity and consistency.

Table 4. Determination of formulations pH and viscosities after preparation of formulations

Gel code	pH	Viscosity (cP)	Torque (%)
F1	6.8	11500	11.6
F2	7.2	19200	9.4
F3	7.4	17500	17.4
F4	7.4	38600	8.4

4. CONCLUSION

Due to its composition, the essential oil of *Matricaria recutita* L. in this study met the recommendations of the pharmacopoeia by its composition, although its concentration of 0.3% v/w was slightly lower than the required minimum of 4 mL/kg (0.4% v/w). Results from the preformulation studies suggest that both placebo formulations mentioned above are suitable to produce an herbal topical gel. It is anticipated that the next research stage will address its anti-inflammatory and antibacterial activities produced by the gels containing chamomile essential oil.

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ALES Grade			
(Other) Grade			

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FORMULATION AND EVALUATION OF HERBAL ORAL GEL WITH MATRICARIA RECUTITA

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INTRODUCTION

Matricaria recutita, otherwise known as chamomile is of the Astaraceae family and is vastly grown in Europe and western Asia. Chamomile is among the most widely used and well-studied herbs in the world. Its floral part has been found to have several pharmacological activities [1,2]. The aim of this study design a herbal formulation with chamomile extract and evaluate it anti-microbial efficacy and stability.

MATERIALS AND METHODS

Materials

The infloroscences of *Matricaria recutita* were collected during flowering stage. Carbopol 940, Triethanolamine, Methyl paraben, Glycerine were purchased from Doga ilac, Turkey. HPMC was purchased from Kimetsan, Turkey.

Isolation of the Essential Oil

Gas Chromatography Mass Spectrometry was done using an Agilent 5977B GC-MSD system. Innowax FSC column (60 m x 0.25 mm. 0.25 µm film thickness) was used with helium as carrier gas (0.8mL/min).

Preparation of Placebo Gels

Preformulation studies was carried out to decide the most suitable gel base depending on the physicochemical properties of the essential oil extract. pH measurement of the gels was carried out using a digital pH meter. Viscosity of the gels was determined using Brookfield viscometer (DV-II+ Pro) at 20 rpm.

Table 1: Placebo gels formulation

Gel code	Carbopol 940P (%)	HPMC (%)	Glycerin (%)	Methyl paraben (%)	Triethanol amine	Purified water (%)
F1	0.5	-	10	0.1	q.s	q.s 100
F2	1	-	10	0.1	q.s	q.s 100
F3	-	2	10	0.1	-	q.s 100
F4	-	2.5	10	0.1	-	q.s 100

RESULTS AND DISCUSSION

A total of 96.8% was identified from the essential oil represented by 4 compounds as seen in Table 2. Placebo formulations with 1% Carbopol 940P and 2.5% Hydroxypropyl methyl cellulose showed good consistency, appearance, and no separation with the pH within the desired range. Both gels showed shear thinning ability; as the shear stress increased, the viscosity decreased.

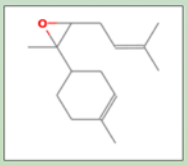

Figure 1: structure of α-bisabolene oxide A

Table 2: Essential oil composition of *M. Recutita*

LRI	Compound name	Rel. percentage amount (%)
1358	Artemisia ketone	3.7
2217	α-bisabolene oxide A	82.5
2444	Chamazulene	7.6
2446	α-bisabolol oxide A	3.0

Table 3 : pH and Viscosity values at 25°C

Gel code	pH	Viscosity (cP)	Torque (%)
F1	6.8	11500	11.6
F2	7.2	19200	9.4
F3	7.4	17500	17.4
F4	7.4	38600	8.4

CONCLUSION

Results from the preformulation studies suggest that both placebo formulations mentioned above are suitable to produce a herbal topical gel. It is anticipated that the next research stage will address the its anti-inflammatory and anti-bacterial activities produced by the gels containing chamomile essential oil.

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