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ORIGINAL ARTICLE / ÖZGÜN MAKALE

ANTIMICROBIAL COMBINATION OF *LAVANDULA ANGUSTIFOLIA* L. ESSENTIAL OIL WITH KOJIC ACID

KOJİK ASİT İLE LAVANDULA ANGUSTIFOLIA L. UÇUCU YAĞININ ANTİMİKROBİYAL KOMBİNASYONU

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ABSTRACT

Objective: *Lavandula angustifolia L. (Lavender) is one of the most plants essential oils used in the cosmetic, food and biological activities. Kojic acid has been used in cosmetics for its whitening effect and pharmaceutical activity. The aim of this study to determine the composition of the Pharmacopoeia quality L. angustifolia essential oil (EO). Moreover, antimicrobial activities against skin pathogens and synergistic antibacterial activity were also examined of EO and kojic acid.*
Material and Method: *In this work, chemical composition of the EO was defined. Linalyl acetate (43.3%) and linalool (38.6%) were determined as the major components by GC-MS and GC-FID, simultaneously. The antimicrobial activity was evaluated against Candida albicans, C. glabrata, Staphylococcus aureus and Salmonella typhimurium.*
Result and Discussion: *EO and kojic acid showed weak antimicrobial effects. MIC values were determined as the EO 10 mg/ml and kojic acid 1.25 mg/ml against S. typhimurium. To assess the synergistic activity was evaluated by the checkerboard microdilution assay, EO was combined with kojic acid against S. typhimurium. Among the tested skin pathogen microorganisms, S. typhimurium was more sensitive to kojic acid. Therefore, synergic activity was investigated against S. typhimurium and found indifferent effect.*
Keywords: *Antimicrobial activity, kojic acid, Lavandula angustifolia, synergistic activity*

ÖZ

Amaç: *Lamiaceae familyasına ait bir bitki olan Lavandula angustifolia L. (Lavanta), kozmetik, yiyecek ve biyolojik etkilerinden dolayı en çok kullanılan uçucu yağlardan birisidir. Kojik asit beyazlatıcı etkisi için kozmetikte ve antimikrobiyal, antibakteriyel, antiviral gibi farmasötik etkilerinden dolayı kullanılmaktadır. Bu çalışmanın amacı Farmakope kalitesindeki Lavandula angustifolia uçucu yağının kimyasal kompozisyonunu belirlemektir. Buna ek olarak cilt patojenlerine karşı antimikrobiyal aktivitesi ve kojik asit ile uçucu yağın aktivite olarak antibakteriyel sinerjisi incelenmiştir.*
Gereç ve Yöntem: *Bu çalışmada, uçucu yağın kimyasal bileşimi araştırılmıştır. Uçucu yağın içerdiği ana bileşenler GK-AİD ve GK-KS ile linalil asetat (%43,3) ve linalol (%38,6) olarak tespit edilmiştir. Antimikrobiyal aktivite Candida albicans, C. glabrata, Staphylococcus aureus ve Salmonella typhimurium'a karşı değerlendirildi.*
Sonuç ve Tartışma: *Uçucu yağ ve kojik asit C. albicans ve S. aureus'a karşı zayıf antimikrobiyal*

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etki gösterdi. MİK değerleri S. typhimurium'a karşı uçucu yağda 10 mg/ml ve kojik asit 1,25 mg/ml olarak hesaplandı. Sinerjik aktiviteyi değerlendirmek için dama tahtası mikrodilüsyon yöntemi ile uçucu yağ kojik asit ile S. typhimurium'a karşı birleştirildi. Test edilen cilt patojen mikroorganizmalar arasında S. typhimurium, kojik aside karşı daha duyarlıdır. Bu nedenle S. typhimurium'a karşı sinerjik aktivite araştırıldı ve bağımsız etki gözlemlenmiştir.
Anahtar Kelimeler: *Antimikrobiyal aktivite, kojik asit, Lavandula angustifolia, sinerjik aktivite*

INTRODUCTION

The overuse and misuse of antibiotics were resulted in the creation of antibiotic-resistant microorganisms, making treating infectious diseases more challenging. However, essential oils have emerged as a potential solution to combat bacterial antibiotic resistance. Essential oils are multi-component and have been observed to have a synergistic effect when combined with antibiotics, decreasing the minimal effective dose of antibiotics, and limiting their adverse effects. Studies have shown that essential oils can affect both the external envelope of the cytoplasm and cell of microorganisms, leading to a disturbance in their structures and functions, ultimately rendering them permeable [1]. Essential oils have been found to inhibit multidrug-resistant bacteria independently of their antibiotic resistance profile, and their effectiveness against common pathogens depends on the concentration of active phenolic compounds [2]. Therefore, the essential oils' combination with conventional antibiotics has great promise for the development of novel treatments and the treatment of infectious disorders caused by multidrug-resistant pathogens [1].

Lavandula angustifolia L. (Lavender), plant is family name Lamiaceae, is used in the cosmetics, food, pharmaceuticals, and biological activities, such as antioxidant effect. Among its biological activities beside the central nervous system are antimicrobial, antioxidant and anti-inflammatory activities [3,4].

Kojic acid is one of the popular ingredients used in various cosmetic products due to its whitening effects on the skin and against sunspots, inhibits catecholase activity of tyrosinase and pharmaceutical activity. Kojic acid is a natural product by several species of fungi like *Penicillium* and *Aspergillus.* Whereas the natural kojic acid is used in cosmetics for skin whitening purposes and reducing sunspots. It also functions as an antioxidant caused by free radicals on the skin along with a broad spectrum of antimicrobial effects. It is a potent natural antioxidant, mild anti-inflammatory safe compound without genotoxic properties [5,6].

The current investigation aimed to identify the antimicrobial properties of pharma-grade *Lavandula angustifolia* essential oil with kojic acid as a combination against human skin pathogens. Initially the EO was confirmed as linalyl acetate (43.3%) and linalool (38.6%) were identified as the major components. The antimicrobial activity was evaluated against *Escherichia coli, Candida albicans, C. krusei, Staphylococcus aureus* and *Salmonella typhimurium.* Both the oil and kojic acid showed weak antimicrobial effects against *C. albicans* and *S. aureus*. To assess the antimicrobial combination activity a checkerboard microdilution assay was conducted. To the best our knowledge, the synergistic activity of EO and kojic acid was observed for the first time against pathogens like *Salmonella typhimurium.*

MATERIAL AND METHOD

General Experimental Procedures

Lavandula angustifolia (Pharma Grade, Davenne, France) analytical compounds and microbiological media were obtained from Sigma-Aldrich, Merck, Fluka if not otherwise stated in high purity.

GC-FID and GC/MS Analysis

The essential oil was analysed to confirm its quality by GC-FID and GC-MS, at the same [7-9]. Main components were compared with European Pharmacopoeia 8th Edition.

An Agilent 5975 GC-MSD equipment was used for the GC-MS analysis. Helium (0.8 ml/min)

was utilized as the carrier gas. The gas chromatograph's oven degree was kept constant at 60-240°C at a rate of 1°C/min. The mass spectrum was *m/z* 35 to 450.

An Agilent 6890N GC equipment was used for the GC analysis. To achieve the same elution order using GC-MS, simultaneous auto-injection on the same column under the same operating conditions was performed. FID chromatograms were used to compute the relative percentage quantities of the separated compounds.

Identification of the Volatile Components

The volatile components were identified by comparing their relative retention durations to those of authentic samples or their relative retention index (RRI) to a *n*-alkanes' series. Computerized scanning against commercial databases (Wiley GC-MS and MassFinder 4.0 Libraries) [7,8] and the in-house "Başer's Essential Oil Constituents Library" comprised of actual compounds and components of recognized oils.

Microorganisms

The human skin test pathogens used in the study were *Salmonella typhimurium* American Type Culture Collection (ATCC) 14028, *Escherichia coli* Research Service Culture Collection (NRRL) B-3008, *Candida albicans* ATCC 90028 *and Candida krusei* ATCC 6258.

Antimicrobial Activity

Minimum inhibitory concentrations of the oil and kojic acid that producing 50% of inhibition (MIC50) were determined using Clinical and Laboratory Standards Institute (CLSI) methods with adaptations for aerobic microorganisms (M07-A7 and M27-A2), also European Committee of Antimicrobial Susceptibility Testing (EUCAST E.DEF 7.2) was used [10,11].

Synergistic Antibacterial Activity

The Checkerboard microdilution assay was used in 96-well plates to study the interaction of the test samples. There were eight successive dilutions of *Lavandula angustifolia* essential oil and antibiotic tetracycline (128-0.25 g/ml) produced. The broth microdilution checkerboard technique was utilized, and the fractional inhibitory concentration index (∑FIC) was calculated as the total of the MICs of each sample when used in combination divided by the MIC of the sample when used alone [12]. As a result, the following activity kinds were defined [13]:

Synergism: $\sum FIC \leq 0.5$

Additive effect: $\sum FIC\ 0.5 \leq 1$

Indifferent effect: $\sum FIC > 1–4$

Antagonism: $\sum FIC \geq 4$.

RESULT AND DISCUSSION

Chemical Composition

In this present study, Pharmacopoeia grade essential oil from commercial sources was evaluated for its broad antibacterial properties. The essential oil was analysed to confirm its quality. Linalyl acetate (43.3%) and linalool (38.6%) were determined as major components. Other constituents were listed in Table 1. According to result, the essential oil was complied with the supplier's quality and Pharmacopoeia Monograph (2014). Furthermore, the main constituents are oxygenated monoterpenes.

The chemical composition of *Lavandula angustifolia* essential oil can vary depending on various factors such as the plant genotype, environmental conditions, and part of the plant used. However, some common components were identified in the *L. angustifolia*'s oil. The main components of this essential oil are often linalool, linalyl acetate, geraniol, *β*-caryophyllene, and lavandulyl acetate. The percentage of each component can vary, but linalool and linalyl acetate are typically present in significant amounts.

Table 1. The volatile components of *L. angustifolia*

No	**RRI[a]**	**Compound**	**%[b]**
1	1032	*α*-Pinene	0.1
2	1076	Camphene	0.3
3	1118	*β*-Pinene	0.1
4	1132	Sabinene	tr
5	1146	*δ*-2-Carene	0.3
6	1174	Myrcene	0.3
7	1203	Limonene	0.2
8	1213	1,8-Cineole	0.1
9	1230	*n*-Butyl-*n*-butyrate	0.1
10	1246	*(Z)-β*-Ocimene	0.8
11	1265	3-Octanone	1.5
12	1266	*(E)-β*-Ocimene	0.3
13	1280	*p*-Cymene	0.1
14	1282	Hexyl acetate	0.6
15	1386	1-Octenyl acetate	0.7
16	1393	3-Octanol	0.3
17	1424	Hexyl butyrate	0.4
18	1450	*trans*-Linalool oxide (*furanoid*)	0.3
19	1452	1-Octen-3-ol	0.4
20	1478	*cis*-Linalool oxide (*furanoid*)	0.3
21	1532	Camphor	0.6
22	1553	**Linalool**	**38.6**
23	1565	**Linalyl acetate**	**43.3**
24	1583	*α*-Santalene	0.9
25	1595	*trans-β*-Bergamotene	0.2
26	1612	*β*-Caryophyllene	3.8
27	1695	*(E)-β*-Farnesene	1.4
28	1706	*α*-Terpineol	0.6
29	1719	Borneol	2.0
30	1733	Neryl acetate	0.2
31	1765	Geranyl acetate	0.4
32	1808	Nerol	tr
33	1857	Geraniol	0.1
34	2008	Caryophyllene oxide	0.7
		Monoterpene hydrocarbons	**2.5**
		Oxygenated monoterpenes	**87.4**
		Sesquiterpene hydrocarbons	**6.3**
		Oxygenated sesquiterpenes	**0.7**
		Others	**3.1**
		Total	**100**

tr: Trace (<0.1 %); [a]: Relative retention indices calculated against *n*-alkanes; [b]: calculated from FID data

For example, one study reported linalool at 30.6% and linalyl acetate at 14.2%, while another study found linalyl acetate at 27.5% and linalool at 24.1% [14,15]. These components contribute to the characteristic aroma and potential therapeutic properties of *Lavandula angustifolia* essential oil.

Antimicrobial Activity

The antimicrobial abilities of essential oils and their volatile components are critical in utilizing them. Thus, in the frame of our study, the antimicrobial effect of the *Lavandula* essential oil and kojic acid were tested on different *in vitro* antimicrobial assays. MIC values were listed on Table 2. According to the results, kojic acid was showed higher antibacterial and antifungal properties than essential oil. When the results were compared, it was observed that both kojic acid and essential oil had inhibitory effects against *Salmonella typhimurium*.

Table 2. Antimicrobial activities of Kojic acid and *L. angustifolia* as MIC (mg/ml)

Bacterial strains	**Kojic acid**	***L. angustifolia***	**Ampicilin**	**Clarithromycin**	**DMSO**
E. coli NRRL B-3008	2.5	2.5	0.01	0.02	-
S. typhimurium ATCC 14028	1.25	5	1.3	0.04	-
Yeast isolates			**Ketoconazole**	**Itraconazole**	**Fluconazole**
Candida albicans ATCC 90028	>1.25	10	0.01	0.04	0.05
C. krusei ATCC 6258	>1.25	2.5	0.01	0.01	0.04

The antimicrobial effect of kojic acid against several microorganisms has been reported. Previous research explored kojic acid's antibacterial and anti-biofilm action against some foodborne pathogens like *Listeria monocytogenes*, and *S. typhimurium*. The study showed that *Escherichia coli* was significantly susceptible, with the lowest MIC (10 mM) and MBC (20 mM) [16]. Another study found that kojic acid had antibacterial effect against *P. aeruginosa*, *S. aureus*, and *Micrococcus luteus* with minimum inhibitory concentration values between 0.125 and 1.0 mg/ml [17]. These findings suggest that kojic acid has potential as an antimicrobial agent against various bacteria.

Lavandula essential oil was demonstrated to have considerable antibacterial properties against a wide range of microorganisms. In previous research evaluated the antimicrobial activity of EOs from different *Lavandula* cultivars and found that they showed antimicrobial activity against all microorganisms analysed, indicating the broad-spectrum antimicrobial potential of *Lavandula* essential oil [18]. Another study found that Lavandula angustifolia essential oil had an antibacterial effect against *Staphylococcus* species in a hospital setting, decreasing germs in all hospital places [19]. These findings highlight the significant antimicrobial activity of *Lavandula* essential oil, indicating its potential for various applications in antimicrobial formulations.

Synergistic Antibacterial Activity

The essential oil and kojic acid were combined varying proportions to determine the synergistic antibacterial potential. Antibacterial combination results were expressed as the fractional inhibitory concentration index (ΣFIC). Combined with kojic acid essential oil has an additive effect (ΣFIC: 0.5078) (Table 3.).

Kojic acid has been found to have synergistic antibacterial activity when combined with other compounds. For example, a study found that kojic acid and tea polyphenols had a strong synergistic antibacterial effect against spoilage bacteria in refrigerated sea bass fillets [20]. Another study investigated the potential antibacterial properties of kojic acid in conjunction with metal cations by co-crystallizing them and reported that co-crystallization of kojic acid with silver(I), copper (II), zinc (II), and gallium (III) demonstrated increased antibacterial activity [21]. Furthermore, kojic acid-grafted

konjac glucomannan oligosaccharides were reported to have high antimicrobial effects against bacteria like *S. aureus* in a study [22]. These findings suggest that kojic acid can enhance the antibacterial activity of other compounds, making it a potentially useful ingredient in antibacterial formulations.

Table 3. Fractional Inhibitory Concentration Index (ΣFIC) (µg/ml)

Bacteria	**Kojic Acid**			***L. angustifolia* Essential Oil**				
	***A**	****C**	**FIC**	**A**	**C**	**FIC**	**ΣFIC**	**RESULT**
S. tymphirium	1.25	0.625	0.5	5	0.039	0.0078	0.5078	**Additive effect**

*A: MIC values of alone, **C: MIC values in combination

Lavandula essential oil was found to have synergistic antibacterial activity when combined with other compounds. In previous study found that the combination of *L. latifolia* essential oil and camphor had a synergistic antibacterial effect [23].

Another study examined the possible synergy of essential oils from *Lavandula angustifolia*, *Artemisia herba alba*, and *Rosmarinus officinalis*. The study found that combining these essential oils exhibited synergistic antibacterial effects against various bacterial strains. [24].

These findings indicate that *Lavandula* essential oil can enhance the antibacterial activity of other compounds, making it a potentially helpful ingredient in antibacterial formulations.

The literature did not return specific information about the synergistic effects of kojic acid and *Lavandula* essential oil. However, it is known that both kojic acid and *Lavandula* essential oil have antimicrobial and antioxidant activities. Kojic acid has been found to possess antifungal activity, while *L. angustifolia* essential oil has demonstrated antimicrobial and antioxidant activities. Our research has shown that the additive effect of kojic acid and *Lavandula* essential oil was determined.

Among the tested the pathogen microorganisms, *S. typhimurium* was more sensitive to kojic acid and *L. angustifolia*. Therefore, synergic activity was investigated against *S. typhimurium* and found additive effect. In the present work, to the best of knowledge there is no report for kojic acid and combination with *L. angustifolia*. Further studies are required for the safe therapeutic *in vivo* and clinical studies.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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