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ORIGINAL ARTICLE / ÖZGÜN MAKALE

EVALUATION OF THE ANTIBACTERIAL ACTIVITIES OF NATURAL COUMARINS FROM APIACEAE PLANTS

APIACEAE BİTKİLERİNDEN ELDE EDİLEN DOĞAL KUMARİNLERİN ANTİBAKTERİYEL AKTİVİTELERİNİN DEĞERLENDİRİLMESİ

Fatma TOSUN[1], Ayşegül HOŞ[2]*, Ayşe İNCİ[2], Ayşe ÇALIŞ[2], Feyyaz MIHOĞLUGİL[3], Demet AKALGAN AKLAR[4], Mahmut MİSKİ[5]

[1]Istanbul Medipol University, School of Pharmacy, Department of Pharmacognosy, 34810, Istanbul, Türkiye
[2]Istanbul Medipol University, School of Pharmacy, Department of Pharmaceutical Microbiology, 34810, Istanbul, Türkiye
[3]Bahçeşehir Cyprus University, Faculty of Pharmacy, 99258, Nicosia, Northern Cyprus
[4]Istanbul University-Cerrahpaşa, Faculty of Pharmacy, Department of Pharmacy Business Administration, 34116, Istanbul, Türkiye
[5]Istanbul University, Faculty of Pharmacy, Department of Pharmacognosy, 34116, Istanbul, Türkiye

ABSTRACT

Objective: *This study aimed to determine the antibacterial activity of fourteen natural coumarin derivatives against various bacterial strains including Enterococcus faecalis (ATCC 29212), Staphylococcus aureus (ATCC 6538), Staphylococcus epidermidis (ATCC 12228), Escherichia coli (ATCC 8739), and Salmonella enterica serovar Typhimurium (ATCC 14028).*
Material and Method: *The antibacterial activity of the following fourteen natural coumarins: 4'-senecioyloxyostol (1), deltoin (2), smyrnioridin (3), karatavicinol (4), badrakemin (5), colladonin (6), badrakemone (7), colladonin acetate (8), anatolicin (9), 14'-hydroxycolladonin (10), 14'-hydroxybadrakemin (11), 14'-acetoxycolladonin (12), 14'-acetoxybadrakemone (13), and 14'-acetoxybadrakemin (14) was investigated by the disc diffusion method.*
Result and Discussion: *Among the microorganisms tested, Staphylococcus epidermidis showed the highest sensitivity to coumarin derivatives, while Escherichia coli was the least sensitive. Colladonin and colladonin acetate showed activity against all bacterial strains tested, except E. coli and S. enterica serovar Typhimurium, respectively. In particular, 4'-senecioyloxyostol exhibited the strongest antibacterial activity at a concentration of 64 µg/disc, with zones of inhibition ranging from 6.6 to 7.5 mm.*
Keywords: *Antibacterial, Apiaceae, biological activity, coumarin, disc diffusion method*

ÖZ

Amaç: *Bu çalışmanın amacı, on dört doğal kumarin türevinin Staphylococcus epidermidis (ATCC 12228), Staphylococcus aureus (ATCC 6538), Enterococcus faecalis (ATCC 29212), Escherichia coli (ATCC 8739) ve Salmonella enterica serovar Typhimurium (ATCC 14028) bakteri suşlarına karşı antibakteriyel aktivitesini değerlendirmektir.*
Gereç ve Yöntem: *On dört doğal kumarinin antibakteriyel aktivitesi: 4'-senecioyloxyostol (1), deltoin (2), smyrnioridin (3), karatavicinol (4), badrakemin (5), colladonin (6), badrakemone (7), colladonin acetate (8), anatolicin (9), 14'-hydroxycolladonin (10), 14'-hydroxybadrakemin (11),*

* **Corresponding Author / Sorumlu Yazar:** Ayşegül Hoş
e-mail / e-posta: aysegulhos@medipol.edu.tr, **Phone / Tel.:** +902166812260

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14'-acetoxycolladonin (12), 14'-acetoxybadrakemone (13) ve 14'-acetoxybadrakemin (14) disk difüzyon yöntemi kullanılarak belirlenmiştir.
Sonuç ve Tartışma: *Test edilen mikroorganizmalar arasında, Staphylococcus epidermidis kumarin türevlerine karşı en yüksek duyarlılığı gösterirken, Escherichia coli en az duyarlılık gösteren suş olarak belirlenmiştir. Colladonin ve colladonin asetat, sırasıyla E. coli ve S. enterica serovar Typhimurium bakterilerine karşı antibakteriyel aktivite göstermezken, test edilen diğer tüm bakteri suşlarına karşı antibakteriyel aktivite göstermiştir. Özellikle, 4'-senecioyloxyostol 64 µg/disk konsantrasyonunda en güçlü antibakteriyel aktiviteyi 6.6 -7.5 mm zon çapları ile göstermiştir.*
Anahtar Kelimeler: *Antibakteriyel, Apiaceae, biyolojik aktivite, disk difüzyon yöntemi, kumarin*

INTRODUCTION

People have used natural remedies to treat diseases since ancient times, and many contemporary medicines have been developed using natural product leads [1].

The screening of plant extracts and natural products is still offering the best choices for finding new structures that could lead to active agents in various human diseases. Researchers are actively working on discovering and developing new drugs from natural product sources to treat numerous illnesses [2-5].

It was reported that approximately 50,000 men, women, and children die of microbial infections around the world every day, and 700 thousand deaths occur yearly from multidrug-resistant (MDR) bacterial strains [6,7,8]. The increasing antibiotic resistance of microorganisms has revived intensive studies on the antimicrobial activities of many plant extracts and phytochemicals as alternative strategies for treating bacterial infections [1,9,10].

Phenolic acids, tannins, quinones, saponins, terpenoids, flavonoids, coumarins, and alkaloids found in natural resources are reported to be responsible for antimicrobial activity [11].

Coumarins are the largest class of 1-benzopyran derivatives and a significant group of natural compounds widely distributed in a large number of plants and have several biological activities that include anti-inflammatory, anticoagulant, antibacterial, antimycobacterial, antioxidant, antifungal, antiviral, anticancer, antihypertensive, anticonvulsant, antiadipogenic, antiallergic, anticholinesterase and antihyperglycemic [12-16]. It was reported that more than 1300 coumarin derivatives have been isolated from natural resources [5]. Several coumarin derivatives have clinical applications, such as warfarin, phenprocoumon, and acenocoumarol are well-known as potent anticoagulant agents; novobiocin and armillarisin A are antibiotics; ensaculin is also well-known for its anti-dementia effects; and hymecromone is a choleretic and antispasmodic agent [6]. Antibacterial activities of natural and synthetic coumarin derivatives against several microorganisms have been reported [7,14,17-33].

As a part of our investigations on the biological activities of coumarins, 14 natural coumarin derivatives, namely 4'-senecioyloxyostol (**1**), deltoin (**2**), smyrnioridin (**3**), karatavicinol (**4**), badrakemin (**5**), colladonin (**6**), badrakemone (**7**), colladonin acetate (**8**), anatolicin (**9**), 14'-hydroxycolladonin (**10**), 14'-hydroxybadrakemin (**11**), 14'-acetoxycolladonin (**12**), 14'-acetoxybadrakemone (**13**) and 14'-acetoxybadrakemin (**14**) (Fig. 1), were examined for their antimicrobial activities against *E. coli* (ATCC 8739), *S. aureus* (ATCC 6538), *E. faecalis* (ATCC 29212), *S. epidermidis* (ATCC 12228), and *S. enterica* serovar Typhimurium (ATCC 14028).

MATERIAL AND METHOD

Coumarin Derivatives

The coumarin derivatives used in this study were isolated from the roots of the following Apiaceae species: *Neocryptodiscus papillaris* (Boiss.) Herrnst. & Heyn; 4'-senecioyloxyostol (**1**); *Petroedmondia syriaca* (Boiss.) Tamamsch; deltoin (**2**), and smyrnioridin (**3**); *Heptaptera anatolica* (Boiss.) Tutin; karatavicinol (**4**), badrakemin (**5**), colladonin (**6**), badrakemone (**7**), anatolicin (**9**), 14'-hydroxycolladonin (**10**), 14'-acetoxybadrakemin (**14**); *Heptaptera cilicica* (Boiss. & Balansa) Tutin; colladonin acetate (**8**), 14'-acetoxycolladonin (**12**), 14'-acetoxybadrakemone (**13**); *Heptaptera triquetra* (Vent.) Tutin; 14'-hydroxybadrakemin (**11**) [34-38].

Determination of Antibacterial Properties

Disc diffusion method was performed to investigate the antibacterial properties of coumarin derivatives [39]. The test microorganisms used in this study *S. epidermidis* (ATCC 12228), *S. aureus* (ATCC 6538), *E. faecalis* (ATCC 29212), *E. coli* (ATCC 8739), and *S. enterica* serovar Typhimurium (ATCC 14028) were obtained from İstanbul Medipol University, School of Pharmacy, Microbiology Research Laboratory.

Test microorganisms were inoculated into Tryptic Soy Broth (Neogen, United Kingdom) and incubated for 24 hours at 37°C. Then, they were inoculated onto 5% Sheep Blood Agar (Becton Dickinson GmbH, Germany) and incubated for 24 hours at 37°C.

The 24h culture was used to obtain a bacterial suspension and adjusted to 0.5 McFarland using a densitometer (Biosan). For the investigation of the antibacterial properties of 14 natural coumarin derivatives, the disc diffusion method was applied (Figure 1). Each of the sterile discs (Bioanalyse, 6 mm in diameter) was impregnated with 20 µl of each natural coumarin derivative. Each of 0.5 McFarland adjusted bacterial suspension was inoculated onto Mueller Hinton Agar (Neogen, United Kingdom) plates with sterile swabs. After that, the impregnated discs were gently pressed onto the inoculated Mueller Hinton Agar plates. The incubation period was 24 hours at 37°C. Finally, the diameters of the inhibition zones (IZs) were measured with a digital caliper. Commercially available antibiotic discs (Amoxicillin 25 µg) were positive control. Discs impregnated with DMSO were used as a negative control. To obtain precise results, assays were performed three times under aseptic conditions. The diameters of the IZs were taken as the average of the three replicates.

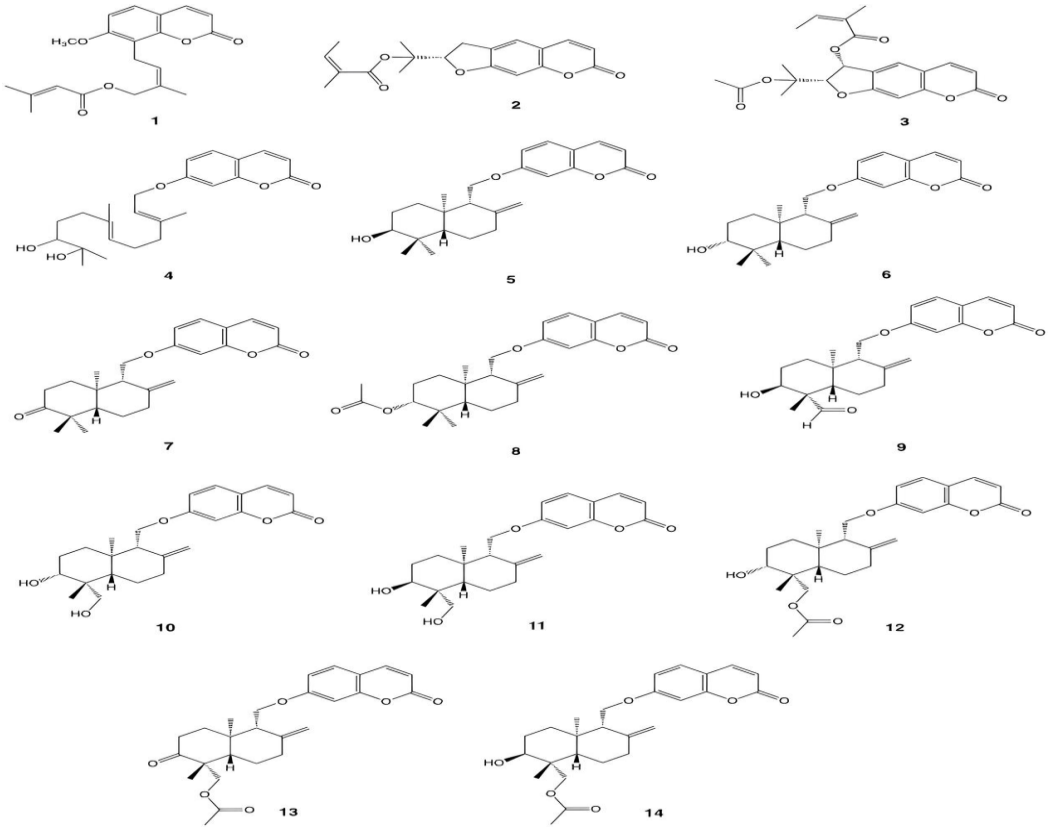

Figure 1. Structures of the natural coumarins from Apiaceae plants used in the antibacterial activity testing [4'-senecioyloxyostol (**1**), deltoin (**2**), smyrnioridin (**3**), karatavicinol (**4**), badrakemin (**5**), colladonin (**6**), badrakemone (**7**), colladonin acetate (**8**), anatolicin (**9**), 14'-hydroxycolladonin (**10**), 14'-hydroxybadrakemin (**11**), 14'-acetoxycolladonin (**12**), 14'-acetoxybadrakemone (**13**) and 14'-acetoxybadrakemin (**14**)]

RESULT AND DISCUSSION

This research study investigated the antibacterial properties of 14 natural coumarin derivatives, namely 4'-senecioyloxyostol (**1**), deltoin (**2**), smyrnioridin (**3**), karatavicinol (**4**), badrakemin (**5**), colladonin (**6**), badrakemone (**7**), colladonin acetate (**8**), anatolicin (**9**), 14'-hydroxycolladonin (**10**), 14'-hydroxybadrakemin (**11**), 14'-acetoxycolladonin (**12**), 14'-acetoxybadrakemone (**13**) and 14'-acetoxybadrakemin (**14**), against *S. epidermidis*, *S. aureus*, *E. faecalis*, *E. coli* and, *S. enterica* serovar Typhimurium. The antibacterial activities of these natural coumarin derivatives against test microorganisms were represented in Table 1.

Table 1. Inhibition zone diameters of 14 natural coumarin derivatives against test microorganisms

Inhibition zone diameters (mm)					
Coumarin derivatives	Test microorganisms				
	S. aureus ATCC 6538	*E. feacalis* ATCC 29212	*S. epidermidis* ATCC 12228	*E. coli* ATCC 8739	*S.* Typhimurium ATCC 14028
Badrakemin (200 µg/disc)	0	0	0	0	0
Colladonin (200 µg/disc)	7.01±1.38	6.36±0.35	6.84±0.33	0	6.67±0.85
14'-acetoxybadrakemin (200 µg/disc)	8.37±0.28	6.44±0.76	7.12±0.53	0	0
Anatolicin (200 µg/disc)	7.72±0.31	0	0	0	0
14'-hydroxycolladonin (200 µg/disc)	6.66±0.57	0	8.16±0.49	0	0
Badrakemone (200 µg/disc)	7.45±0.02	7.50±0.35	9.59±0.56	0	0
Karatavicinol (200 µg/disc)	6.53±0.46	0	9.75±1.88	0	7.59±1.42
4'-senecioyloxyostol (64 µg/disc)	6.64±0.62	0	7.48±0.48	0	7.15±0.34
14'-acetoxycolladonin (200 µg/disc)	0	0	8.17±0.72	7.90±0.02	0
Deltoin (128 µg/disc)	7.62±0.54	0	7.30±0.55	0	6.83±0.72
14'-hydroxybadrakemin (200 µg/disc)	0	8.04±0.34	6.88±0.95	8.97±0.46	0
Colladonin acetate (152 µg/disc)	7.53±0.27	6.32±0.56	7.51±0.40	7.52±0.30	0
14'-acetoxybadrakemone (120 µg/disc)	8.20±1.57	7.10±0.96	7.02±0.12	0	0
Smyrnioridin (320 µg/disc)	0	0	6.51±0.60	0	0
Amoxicillin (25 µg/disc)	19.17±0.79	17.00±0.50	28.53±0.50	20.80±0.2	20.43±0.60
DMSO	0	0	0	0	0

±Standard deviation

In the light of the findings, the most susceptible against the coumarin derivatives used in this study was shown by *S. epidermidis* among the test microorganisms, but *E. coli* has been shown the least susceptibility against the coumarin derivatives. When comparing the antibacterial activity of the coumarin derivatives, colladonin and colladonin acetate showed activity against all the bacteria strains tested except *E. coli* and *S. enterica* serovar Typhimurium respectively. Deltoin, karatavicinol, and 4'-senecioyloxyostol have shown antibacterial activity on the same bacteria, which were *S. aureus, S. epidermidis,* and *S. enterica* serovar Typhimurium. Besides, it was found that 14'-acetoxybadrakemin, badrakemone, and 14'-acetoxybadrakemone have an antibacterial activity against to the same bacteria, which were *S. aureus, E. feacalis,* and *S. epidermidis.* 14'-hydroxycolladonin showed antibacterial activity against to *S. aureus* and *S. epidermidis* whereas 14'-acetoxycolladonin against to *S. epidermidis* and *E. coli.* Anatolicin and smyrnioridin showed activity against only one bacteria strain tested, *S. aureus* and *S. epidermidis*, respectively. Badrakemin showed no inhibition on the all test microorganisms.

In previous studies, the antimicrobial activities of some natural coumarins were determined against to Gram-negative and Gram-positive bacterial strains. They reported that as strongly or moderately active on these microorganisms [27-29,32,33,40-44]. It has been declared that the presence of the prenyl residue leads to increased antibacterial activity of the coumarin derivatives [43,45]. In agreement with these observations, despite its 64 µg/disc concentration, 4'-senecioyloxyostol (a prenylated coumarin derivative) exhibited better antibacterial activity, with inhibition zones ranging from 6.6-7.5 mm (Table 1), which is more potent than the other compounds tested in this study.

Hitherto, deltoin (**2**), and smyrnioridin (**3**), karatavicinol (**4**), badrakemin (**5**), colladonin (**6**), badrakemone (**7**), colladonin acetate (**8**), anatolicin (**9**), 14'-hydroxycolladonin (**10**), 14'-hydroxybadrakemin (**11**), 14'-acetoxycolladonin (**12**), 14'-acetoxybadrakemone (**13**), 14'-acetoxybadrakemin (**14**) have not been tested against the bacteria strains including *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Salmonella* Typhimurium, *Escherichia coli* and *Enterococcus faecalis* and 4'-senecioyloxyostol (**1**) against *Salmonella* Typhimurium. Previously, 4'-senecioyloxyostol has been examined against nine standard strains, including *E. coli* ATCC 10799, *S. epidermidis* ATCC 12228, *S. aureus* ATCC 25923, and *E. faecalis* ATCC 29212, and five clinically isolated strains and found to be active on all test microorganisms [27].

According to our literature research, there is some antibacterial evaluation of natural pyranocoumarins, furanocoumarins, and prenylated coumarins but no study dealing with the antimicrobial activities of the sesquiterpene coumarin derivatives except ferulsinaic acid [27-29,40-44]. Thereby, this is the 1st study on the antimicrobial activities of the sesquiterpene coumarin derivatives tested in this research.

AUTHOR CONTRIBUTION

Concept: F.T., A.H., A.İ., A.Ç.; Design: F.T., A.H., A.İ., A.Ç., M.M.; Control: F.T., A.H., A.İ., A.Ç.; Sources: F.M., D.A.A., F.T., A.H., A.İ., A.Ç.; Materials: F.T., A.H., A.İ., A.Ç., F.M., D.A.A., M.M.; Data Collection and/or Processing: F.T., A.H., A.İ., A.Ç.; Analysis and/or Interpretation: F.T., A.H., A.İ., A.Ç.; Literature Review: F.T., A.H., A.İ., A.Ç., F.M., D.A.A.; Manuscript Writing: F.T., A.H., A.İ., A.Ç., M.M.; Critical Review: F.T., A.H., A.İ., A.Ç., F.M., D.A.A. M.M.; Other: -

CONFLICT OF INTEREST

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

ETHICAL APPROVAL

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

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