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ORIGINAL ARTICLE

# Investigation of the effectiveness of *Syzygium aromaticum*, *Lavandula angustifolia* and *Geranium robertianum* essential oils in the treatment of acute external otitis: A comparative trial with ciprofloxacin

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**KEY WORDS**
Acute external otitis;
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Infection;
Inflammation;

*Background:* Antibiotics and anti-inflammatory agents are the mainstay of acute external otitis (AEO) treatment. The present study investigated the effectiveness of a combination herbal drop (Lamigex) composed of essential oils from *Syzygium aromaticum*, *Lavandula angustifolia*, and *Geranium robertianum* in the alleviation of AEO symptoms and compared its effects to those of ciprofloxacin 0.3% drop.
*Methods:* Seventy patients were randomly assigned to receive ciprofloxacin 0.3% ($n = 35$) or Lamigex ($n = 35$) drop. Each group was administered with three drops every 12 hours for a week. Patients were examined for AEO symptoms and ear discharge cultures at baseline

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*Lavandula angustifolia*;
Pain;
*Syzygium aromaticum*

as well as at the end of trial. Pain severity was also recorded using a visual analogue scale at baseline, the 3rd day, and the 7th day of the trial.
*Results:* All assessed symptoms (tenderness, itching, erythema, edema and discharge) were equally improved in the ciprofloxacin and Lamigex groups by the end of trial ($p > 0.05$). There were remarkable reductions in the visual analogue scale score by the end of trial in both groups ($p < 0.001$). However, the rate of pain improvement was not found to be significantly different between the groups, either at the 3rd or 7th day of trial ($p > 0.05$). The numbers of positive cultures for all tested microorganisms were clearly reduced by the end of the trial in both groups but were not significantly different between the groups ($p > 0.05$).
*Conclusion:* The herbal combination drop that was investigated in the present study exhibited good efficacy in reducing the burden of infection as well as AEO symptoms.


## Introduction

Acute external otitis (AEO) refers to inflammation of the external ear canal[1,2] which affects four out of 100 people every year.[3] This disease occurs under certain conditions involving temperature, humidity, and ambient water. The chief complaint of patients is usually severe unilateral pain and itching of the ear. In the early stages, AEO can cause mild irritation with redness and slight edema in the ear canal. However, at advanced stages, the symptoms would be edema and increased secretions in the ear canal, and might be accompanied by palpable adenopathy localized around and behind the ears.

Severe edema of the ear canal can cause loss of hearing.[2–4] *Pseudomonas aeruginosa* is the most common pathogen for AEO, being responsible for about 40% of illnesses, followed by *Staphylococcus aureus*, which accounts for 9% of AEO cases.[1] Other microorganisms such as *S. epidermidis*, *Proteus* species, *Streptococci*, *Enterococci*, and other Gram-negative bacilli as well as fungi (e.g., *Candida albicans*) have also been reported from AEO cultures.[3–5] The first step in treating AEO is the use of ototopical antibiotics. Other medications include organic acids (e.g., 2% acetic acid) and anti-inflammatory agents (e.g., betamethasone).[2,3] Despite the widespread use of ototopical antibiotics, bacterial resistance is an important concern which necessitates the development of novel therapeutic agents, especially those of natural origin. Heretofore, numerous plants have been reported to possess antibacterial, antiviral, and antifungal properties.[6–12] *Syzygium aromaticum* is a broad-spectrum antimicrobial, anti-inflammatory, analgesic, and healing agent.[13,14] *Lavandula angustifolia* and *Geranium robertianum* are two other medicinal plants which possess antimicrobial and anti-inflammatory properties.[15]

In the present trial, the antimicrobial efficacy of a combination herbal drop composed of essential oils from *S. aromaticum*, *L. angustifolia*, and *G. robertianum* was investigated in patients with AEO and compared to that of ciprofloxacin, a widely used medication.

## Materials and methods

The present study was a noninferiority trial that was designed to indicate that the Lamigex combination herbal drop is at least as effective as ciprofloxacin 0.3% drop (as a standard and widely prescribed drug) in the alleviation of AEO symptoms. Participants were patients aged 18–60 years who were referred to the ENT department of the Baqiyatallah Hospital (Tehran, Iran) with initial AEO symptoms such as pain, itching, edema of the ear canal, tenderness, or irregular ear discharge. Each patient filled out a questionnaire, and the collected information was compiled to study and compare the demographic and laboratory data. The project was approved by the Baqiyatallah University of Medical Sciences (Tehran, Iran) ethics committee, and written informed consent was obtained from the patients.

Patients were randomly assigned to receive a ciprofloxacin 0.3% drop or the herbal combination drop (under the name Lamigex). Each group was administered with three drops every 12 hours for a week. The active ingredients of Lamigex drop were essential oils of *S. aromaticum*, *L. angustifolia*, and *G. robertianum*, which were prepared using a steam distillation method and mixed in equal proportions.[6–8,10] The drops were used after cleansing the ear canal. Randomization was performed individually, and patients were alternatively allocated to treatments encoded as A or B, with the first code being chosen randomly. The patients were allowed to consume analgesics such as acetaminophen or acetaminophen codeine, if necessary, instead of using over-the-counter non-steroidal anti-inflammatory drugs.

Patients were examined for tenderness, itching, irregular discharge, redness, or edema of the ear canal at baseline as well as at the end of trial. The pain score was recorded using a visual analogue scale (VAS) at baseline, the 3rd day, and the 7th day of the trial. The applied VAS was designed as a 100-mm horizontal line without scaling, in which 0 was marked as "no pruritus" and 100 was marked as "unbearable pruritus." Patients were then instructed to place a vertical mark reflecting their pruritus severity. Baseline and post-trial cultures of ear discharge were also investigated. In case of no therapeutic response or worsening of symptoms, administration of Lamigex was immediately discontinued; the patient was then excluded and they subsequently underwent standard treatment (three drops of topical ciprofloxacin every 12 hours).

**Table 1** Baseline and post-trial frequencies of ear discharge cultures in the study groups

| Microorganism | Ciprofloxacin | | Lamigex | |
|---|---|---|---|---|
| | Baseline | 7th day | Baseline | 7th day |
| *P. aeruginosa* | 8 (22.9%) | 0 (0%) | 11 (31.4%) | 1 (2.9%) |
| *S. aureus* | 9 (25.7%) | 2 (5.7%) | 10 (28.6%) | 1 (2.9%) |
| *S. epidermidis* | 7 (20%) | 0 (0%) | 8 (22.9%) | 1 (2.9%) |
| *Streptococcus* spp. | 4 (11.4%) | 1 (2.9%) | 3 (8.6%) | 0 (0%) |
| Other[a] | 7 (20%) | 0 (0%) | 3 (8.6%) | 1 (2.9%) |
| Negative culture | 0 (0%) | 32 (91.4%)[b] | 0 (0%) | 31 (88.6%)[c] |

[a] Including *Escherichia coli*, *Entrococcus* spp., etc.
[b] Statistical analyses did not reveal any significant difference in the post-trial frequencies of negative cultures between the groups ($p = 1.00$).
[c] There were significant reductions in the number of positive cultures in both groups ($p < 0.001$).
Values are number (%) of positive cultures for each microorganism.

## Statistical analysis

Data were analyzed using PASW 18 software and expressed as mean ± SD. Between-group comparisons were performed using independent samples *t*-test (for continuous variables), or chi-square and Fischer's exact tests (for categorical variables). Within-group comparisons of VAS scores were made using repeated-measures ANOVA. A *p* value of $<0.05$ was considered statistically significant.

## Results

Out of the 80 patients who were initially selected for the study, 70 patients (35 in each group) completed the trial, and their questionnaires were included in the final analyses. Exclusion of patients was attributable to being lost to follow-up and not completing the questionnaires. In the ciprofloxacin group, there were 18 males (51.4%) and 17 females (48.6%), whereas 19 males (54.3%) and 16 females (45.7%) completed the trial in the Lamigex group. The mean age of patients was 37.11 ± 8.59 and 37.29 ± 8.65 years in the ciprofloxacin and Lamigex group, respectively. A history of external otitis was reported in 15 (42.9%) patients in the ciprofloxacin group and 13 (37.1%) patients in the Lamigex group, with no significant difference between the groups ($p = 0.626$). In these patients, the interval between the last occurrence of external otitis and current AEO was not significantly different (3.71 ± 5.25 and 3.03 ± 5.38 months in the ciprofloxacin and Lamigex groups, respectively; $p = 0.602$). Likewise, the interval between the onset of symptoms and seeing a physician did not differ between the groups (5.66 ± 2.76 and 5.37 ± 3.13 days in the ciprofloxacin and Lamigex groups, respectively; $p = 0.687$).

The frequencies of positive ear discharge cultures for different pathogenic bacteria are summarized in Table 1. Overall, the numbers of positive cultures for all tested microorganisms were clearly reduced by the end of trial in both groups ($p < 0.001$). The number of positive cultures at the end of trial was not significantly different between the groups ($p = 1.00$).

The groups were comparable in their frequencies of baseline AEO symptoms including tenderness ($p = 0.225$), itching ($p = 0.710$), erythema ($p = 0.163$), edema ($p = 0.743$), and discharge ($p = 0.894$). The improvement of AEO symptoms was evaluated at the end of trial. Interestingly, all assessed symptoms were equally improved in ciprofloxacin and Lamigex groups by the end of trial ($p = 0.678$, 0.626, 0.728, 0.462, and 0.415 for tenderness, itching, erythema, edema, and discharge, respectively) (Table 2). In the same manner, there was no significant difference between the groups regarding the rate of pain

**Table 2** Baseline and post-trial frequencies of acute external otitis symptoms in the study groups

| Symptom | Group | Baseline | *p* | Post-trial severity | | | *p* |
|---|---|---|---|---|---|---|---|
| | | | | Same | Reduced | Completely recovered | |
| Tenderness | Ciprofloxacin | 18 (51.4%) | 0.225 | 0 (0%) | 9 (50%) | 9 (50%) | 0.678 |
| | Lamigex | 23 (65.7%) | | 0 (0%) | 10 (43.5%) | 13 (56.5%) | |
| Itching | Ciprofloxacin | 32 (91.4%) | 0.710 | 3 (9.4%) | 12 (37.5%) | 17 (53.1%) | 0.626 |
| | Lamigex | 30 (85.7%) | | 1 (3.3%) | 12 (40%) | 17 (56.7%) | |
| Erythema | Ciprofloxacin | 24 (68.6%) | 0.163 | 0 (0%) | 8 (33.3%) | 16 (66.7%) | 0.728 |
| | Lamigex | 29 (82.9%) | | 0 (0%) | 11 (37.9%) | 18 (62.1%) | |
| Edema | Ciprofloxacin | 17 (48.6%) | 0.743 | 0 (0%) | 3 (17.6%) | 14 (82.4%) | 0.462 |
| | Lamigex | 20 (57.1%) | | 0 (0%) | 6 (30%) | 14 (70%) | |
| Discharge | Ciprofloxacin | 28 (80%) | 0.894 | 0 (0%) | 6 (42.9%) | 8 (57.1%) | 0.415 |
| | Lamigex | 29 (86.9%) | | 1 (6.2%) | 9 (56.3%) | 6 (37.5%) | |

Values are expressed as number (%) of individuals with the respective symptom.

**Table 3** Frequency of ear pain in the study groups at different time points

| | | Ciprofloxacin | Lamigex | *p* |
|---|---|---|---|---|
| Baseline | | 17 (48.6%) | 19 (54.3%) | 0.632 |
| Day 3 | Same | 1 (5.9%) | 2 (10.5%) | 0.855 |
| | Reduced | 11 (64.7%) | 11 (57.9%) | |
| | Completely recovered | 5 (29.4%) | 6 (31.6%) | |
| Day 7 | Same | 0 (0%) | 0 (0%) | 0.543 |
| | Reduced | 5 (41.7%) | 7 (53.8%) | |
| | Completely recovered | 7 (58.3%) | 6 (46.2%) | |

Values are expressed as number (%).

recovery by either the 3rd ($p = 0.855$) or the 7th ($p = 0.543$) day of the trial (Table 3). Among patients with ear pain, the VAS score was not significantly different between Ciprofloxacin and Lamigex groups at baseline ($p = 0.900$) as well as the 3rd ($p = 0.841$) and the 7th ($p = 0.957$) day of the trial (Fig. 1). However, both groups experienced significant reductions in VAS score and pain severity by the end of the trial ($p < 0.001$) (Fig. 1). The reductions in VAS score in different intervals of the study (days 1–3, 3–7 and 1–7) were also compared between the ciprofloxacin and Lamigex groups. The magnitude of reductions in VAS score was not significantly different between the groups at any of the intervals [days 1–3 ($p = 0.990$), days 3–7 ($p = 0.820$), and days 1–7 ($p = 0.909$)] (Fig. 2).

## Discussion

In order to develop novel medications for AEO, several prerequisites must be met. The most important issues are sufficient coverage of pathogenic microorganisms, and lack of bacterial resistance,[17] allergic reactions, and ototoxicity.[18] One of the most important concerns about the use of ototopical antibiotics is the development of bacterial resistance. Therefore, introduction of herbal preparations with equal efficacy to the currently administered antibiotics is highly desirable to be used alone or in combination with current medications for the purpose of dose reduction and resistance prevention.

In the current study, the combination herbal drop containing essential oils of *S. aromaticum*, *L. angustifolia*, and *G. robertianum* was found to be as effective as ciprofloxacin 0.3% in terms of antibiotic effects as well as reducing AEO-associated pain and symptoms (tenderness, itching, erythema, edema, and discharge).

Clove oil is endowed with multiple medicinal benefits including carminative, antinausea, antivomiting, mouth freshening, analgesic, and sedative effects.[6,14,19] Apart from these effects, clove oil has potent antimicrobial activities against a range of microorganisms such as *S. aureus*, *Klebsiella pneumonia*, *Escherichia coli*, *Enterococcus faceum*, and *C. albicans*.[17–22] Eugenol is the main aromatic component of the clove oil, which is involved in the antimicrobial effects of clove oil.[20,21]

Lavender oil is a well-known and widely used oil which has a broad application in the hygienic and cosmeceutical industries.[22–24] This oil has been the subject of numerous research studies in the past years. These investigations

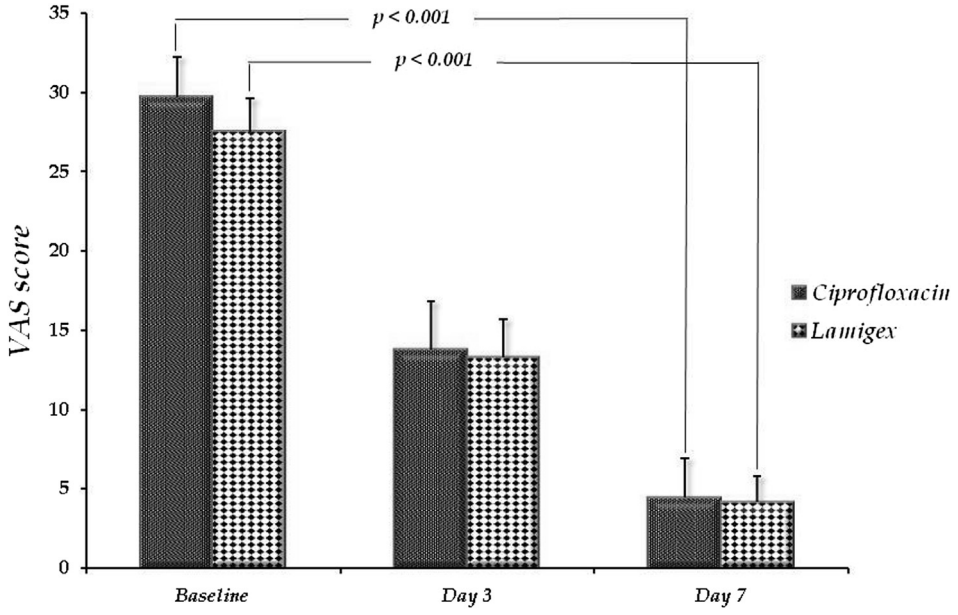


**Figure 1.** Comparison of visual analogue scale (VAS) score between Ciprofloxacin and Lamigex groups.

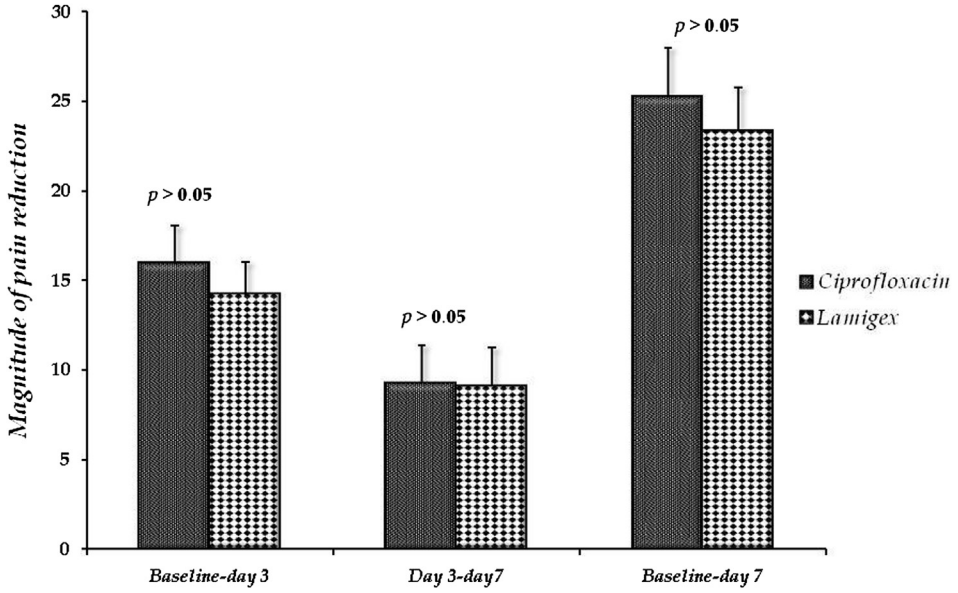


**Figure 2.** Comparison of the magnitude of reduction in VAS score between Ciprofloxacin and Lamigex groups.

have unveiled many medicinal effects for lavender oil including spasmolytic, local anesthetizing, antioxidant, and antibacterial properties.[24–29] Linalool is among the active components of lavender oil which is responsible, at least in part, for the antimicrobial and antifungal properties.[30]

Geraniol and citronellol are the main ingredients of *G. robertianum* oil and have remarkable antifungal activity against the clinical isolates of *C. albicans*. This oil also has fungicidal activity against the toxigenic strains of *Aspergillus flavus* and prevents aflatoxin production. The antifungal activity of geraniol might be attributed to the induction of potassium efflux from the cell and increasing the fluidity of *C. albicans* membrane. Aside from antifungal activity, *G. robertianum* oil has also been shown to exert antibacterial activity against a wide range of Gram-positive and Gram-negative bacteria including *S. aureus*, *P. vulgaris*, *Bacillus cereus*, *S. epidermidis*, *Streptococcus pneumonia*, *K. pneumonia*, *E. coli*, *P. aeruginosa*, and vancomycin-resistant *Enterococcus* species.[6,15,16]

Overall, the herbal combination drop investigated in this study exhibited good efficacy in reducing the burden of infection as well as alleviating AEO symptoms. This finding is especially important when considering the superiority of ciprofloxacin to a number of medications used for the management of AEO. In previous studies, ciprofloxcacin has been demonstrated to have equal or better efficacy compared to classic antibiotic–steroid combination drugs such as oxytetracycline–polymixin B–hydrocortisone and neomycin–polymixin B–hydrocortisone.[31–33] However, further research is warranted to confirm the efficacy of this combination drop in a larger study population. In addition, longer follow-up durations are necessary to assess the possible adverse effects of this drug.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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