# New Synergistic Combination Therapy of Mupirocin and α-Pinene Against Multidrug-Resistant Clinical Strains of Methicillin-Resistant *Staphylococcus aureus*

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**Objective**: Increased mupirocin use leads to mupirocin resistance and is associated with persistence of methicillin-resistant *Staphylococcus aureus* (MRSA) carriers, prolonged hospitalization, and significant economic burdens for health systems. The study aimed to investigate the antimicrobial activity of compounds of *Salvia rosmarinus* L. ("rosemary", formerly *Rosmarinus officinalis*), alone or in combination with mupirocin, against multidrug-resistant MRSA using isolates obtained from pediatric patients.

**Methods**: The *in vitro* antibacterial activity of the monoterpene α-pinene (α-Pi), a rosemary essential oil constituent, alone and in combination with mupirocin, was evaluated by determining the minimum inhibitory concentrations and minimum bactericidal concentrations (MBCs) and the fractional inhibitory concentration indices (FICIs) and fractional bactericidal concentration indices against multidrug-resistant clinical MRSA strains. The *in vivo* efficacy of α-Pi, alone and in combination with mupirocin, to eradicate MRSA infection was determined using an optimized mouse model of MRSA-infected wounds. Mouse skin samples (obtained via biopsy) were assessed for toxicity, and rabbit skin samples for irritation.

**Results**: Both *in vitro* and *in vivo*, α-Pi was active against MRSA strains and acted synergistically with mupirocin against MRSA strains. Mupirocin–monoterpene combinations exhibited FICI values of 0.2 to 0.4, reducing the MBC of topical mupirocin 33-fold. A topical formulation containing α-Pi and mupirocin enhanced the efficacy of mupirocin in an *in vivo* MRSA-infected mouse skin model without significantly harming the skin of mice and rabbits.

**Conclusions**: A topical formulation combining mupirocin and α-Pi may aid in the development of innovative agents for treating MRSA infections.

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*Key words: Alpha-pinene, Methicillin-resistant Staphylococcus aureus, Skin, Mupirocin, Drug synergism*

Despite the use of epidemiological surveillance programs and antimicrobial stewardship programs in health care settings, *Staphylococcus aureus* remains a major health problem worldwide, causing a wide range of infections associated with high morbidity and mortality. Severe infections, especially those caused by methicillin-resistant *S. aureus* (MRSA), including pneumonia and bacteremia, can lead to prolonged hospitalization and a significant economic burden (1).

*S. aureus* is part of the skin flora and can cause potentially severe infections, both in healthcare facilities and in the community (2). Patients with MRSA infections are 64% more likely to die than those with other drug-sensitive bacteria (2).

The antibiotic mupirocin is generally used for the decolonization of *S. aureus* (susceptible and resistant to methicillin) in both patients and healthcare staff. However, the widespread use of mupirocin has put its clinical efficacy a trisk by promoting bacterial resistance (3). Indeed, we reported, for the first time in Argentina, an emerging resistance to mupirocin in clinical isolates from a tertiary pediatric hospital (4).

The World Health Organization has declared that there is a need to find new active agents against resistant bacteria, including MRSA (2). Currently, plant essential oil sand their main constituents are being investigated as possible alternative treatments for the decolonization of MRSA and other skin infections (5,6). Moreover, combinations of plant constituents with antimicrobial agents may have synergistic effects (7).

Previously we demonstrated that a particular constituent of rosemary essential oil, the monoterpene α-pinene (α-Pi), exerts bactericidal effects on *S. aureus* strains susceptible to antibiotics (8). The aim of this study was to investigate the *in vitro* and *in vivo* efficacy of compounds of *Salvia rosmarinus* L. (rosemary, formerly

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*Rosmarinus officinalis*), in particular of this monoterpene, alone and in combination with mupirocin, against multidrug-resistant clinical MRSA isolates obtained from pediatric patients.

## Materials and Methods

### *In vitro* antibacterial activity

A broth microdilution method was used to determine the minimum inhibitory concentration and bactericidal concentration (MIC and MBC, respectively), as previously described (8,9). Two clinical strains of MRSA (MRSA-1977 and MRSA-GM34) were isolated from pediatric patients with bacteremia. The strains were resistant to oxacillin, cefoxitin, erythromycin, clindamycin, gentamicin, ciprofloxacin, levofloxacin, and rifampicin (9,10). A checker board titration assay was used to study the interaction between the plant compound and mupirocin (11). A negative (media without bacteria) and a positive (bacteria without antimicrobials) control were included. The fractional inhibitory concentration (FIC) was determined to be the combination`s MIC/ compound alone`s MIC. Interactions were calculated as the FIC index (FICI) and fractional bactericidal concentration index (FBCI) corresponding to the sum of the FIC and the FBC (FICI/ FBCI = FICA (fractional inhibitory concentration of compound A, α-Pi /FBCA (fractional bactericidal concentration of compound A, α-Pi) + FICB (fractional inhibitory concentration of compound B, mupirocin)/FBCB (fractional bactericidal concentration of compound B, mupirocin); FICI/FBCI ≤0.5 synergistic, >0.5–1 additive, >1 to <4 indifferent, and ≥4antagonistic) (10). Stock solutions of 80% v/v of α-Pi (Moelhausen, Italy) were prepared with 96% ethanol and then dissolved in Muller–Hinton medium containing 0.5% Tween 80 (v/v) plus 5% ethanol.

### Superficial staphylococcal infection model in mice

The experimental procedures were approved by the Institutional Review Board and the Institutional Committee on the Use and Care of Experimental Animals of Garrahan Pediatric Hospital, BuenosAires, Argentina (Protocol ID #011-031).

In accordance with modern animal experimentation guidelines, the minimum number of specimens required to obtain valid results was used, even though this may have been insufficient for statistical validity. In this context, if the results are sufficiently clear and uniform, it is possible to draw conclusions of interest (12). If necessary, based on our results, subsequent experiments may be run to thus improve the level of evidence. This observation also applies to the dermal irritation test.

A superficial skin infection model in mice was used, as previously described (13). The MRSA infection on the skin of the BALB/c mice (n = 7–10) was initiated by inoculation with $10^4$ to $10^5$ cells from an overnight bacterial culture in the stationary phase. An ointment (25 to 30 mg) containing the plant compound mupirocin (Forbenton Co. Laboratories S.A., Argentina) or the vehicle (5% ethanol plus 1% Tween 80) was applied at 4, 6, 8, 24, and 36 hours, post-infection. The animals were sacrificed at 48 hours, post-infection. The wounded skin are as were removed and homogenized in PBS, followed by the recovery of the colony-forming units (CFU) per wound. Biopsies were performed in parallel samples of wounded skin are asstained with hematoxylin-eosin or the Brownand Brenn method. The samples were examined in a blinded fashion under a light microscope (Nikon Eclipse E400, Nikon Industries Inc., Melville, NY 11747).

### Dermal irritation test

The local dermal irritation test was performed in agreement with the guidelines of the Organization for Economic Cooperation and Development (OECD404) (14). Two 4-$cm^2$ areas of dorsal skin from New Zealand white rabbits (n=3) were treated with 3 doses of a topical cream containing either the antimicrobials or the vehicle at 0, 24, and 48 hours under a protocol approved by the Garrahan Pediatric Hospital Institutional Animal Care and Use Committee (IACUC, Protocol ID #765). The severity of skin erythema was scored at 72 hours, post-exposure, and the response was compared to that of the skin of animals receiving only the vehicle or distilled water (untreated animals). Edema was quantified measuring the thickness of the dermis by ultrasonography (Toshiba Xario), using a multi-frequency linear transducer (7–14MHz) that produced at least 20 images of each area of skin.

### Statistical analysis

All the values represent the means (±SD). For statistical analysis, 1-way analysis of variance (ANOVA) was used followed by the 1-way parametric Tukey test and the non parametric Kruskal–Wallis test using the statistical software Prism (GraphPad Software, SanDiego, CA, USA). Differences were considered significant when *P* values were less than .05.

## Results

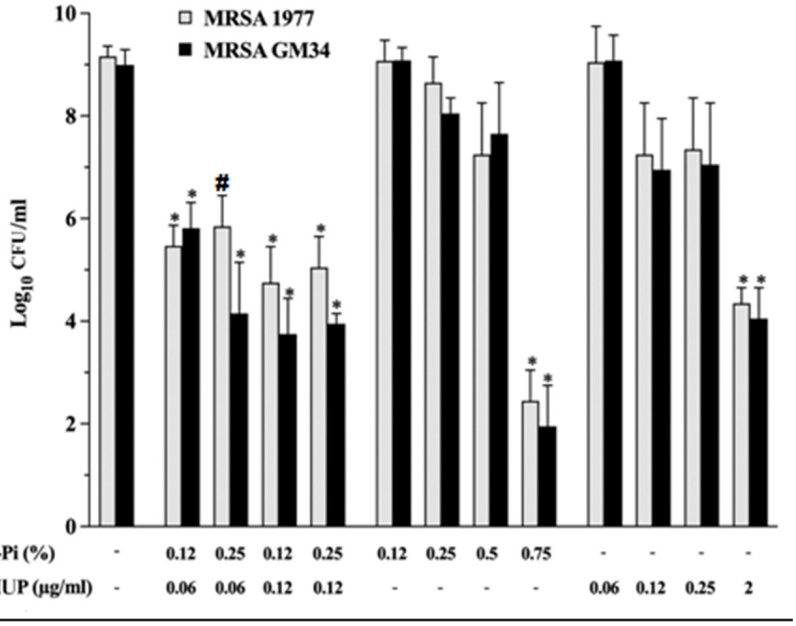
### *In vitro* testing of synergistic antibacterial activity

Figure 1 shows the antimicrobial activity of α-Pi and mupirocin, alone and in combination, against 2 clinical MRSA isolates with multiple resistance to common antibiotics. α-Pinene and mupirocin exhibited MIC values of 0.5% (v/v) and 0.25μg/ml, respectively, against both MRSA clinical isolates, while the MBC values were 0.75% (v/v) and 2 μg/ml, respectively. The binary mixtures containing subinhibitory concentrations of α-Pi and mupirocin revealed that 0.12% α-Pi plus 0.06 μg/ml of mupirocin had an FICI of 0.5, indicating that both antimicrobials interact synergistically at concentrations equivalent to ¼ MIC. Other combinations tested also exhibited additive effects. Interestingly, the combination of 0.5% (v/v) α-Pi and 0.06 μg/ml of mupirocin reduced the MBC value of mupirocin 33-fold yielding FBCI value of 0.2, demonstrating a synergistic interaction between both antimicrobials. Indeed, all the combinations tested showed enhancement of the topical antibiotic. Therefore, it can be deduced that α-Pi strongly increased the effectiveness of mupirocin against both clinical MRSA isolates.

### *In vivo* antimicrobial evaluation in a MRSA skin infection mouse model

In order to explore the effectiveness of a novel antibacterial drug candidate, it is crucial to evaluate the drug's *in vivo* performance. Here, we assess an experimental formulation containing α-Pi, alone and incombination with mupirocin, using an optimized mouse model of staphylococcal skin infection (12). After the bacterial

**Figure 1**. Effect of α-pinene (α-Pi), alone and in combination with mupirocin (MUP), on cell viability of methicillin-resistant *Staphylococcus aureus* MRSA 1977 and MRSA GM-34 clinical isolates after 24h. Error bars represent the SDs of 3 independent experiments. Significant differences **P*<.01 or #*P*<.05 compared to controls without treatment (ANOVA with Bonferroni post-hoc test). CFU=colony-forming units.




vehicle, while α-Pi alone was not effective. In contrast, mupirocin alone only showed mild antibacterial activity.

## Evaluation of adverse effects

A histopathological analysis of the biopsies of the mouse skin without any treatment or treated with the formulation containing the vehicle (1% Tween 80 and 5% ethanol) and the ointment containing the highest concentration of the plant compounds (10 x MIC α-Pi) was performed. Figures 3B and3E show representative samples of biopsies of specimens treated with the vehicle. A mixed inflammatory response (mononuclear cells and neutrophils) in the dermis and hypodermis, slight edema, and bacteria grouped in the corneal layers of the epidermis in comparison with the normal epidermal layer of the skin without any treatment (Fig.3A) can be seen. This effect was probably caused by the initial removal of the upper epidermal layers during the wounding of the skin of the animal, which was done to eliminate the barrier effect of the skin removed by tape stripping. After treatment with 2% mupirocin, mild mixed inflammation in the dermal and hypodermal layers in 3

inoculation of the wounded areas, the ointment was topically applied at 4, 6, 8, 24, and 36 hours, post-infection (Fig.2A). Two series of experiments were performed. In the first, the antibacterial efficacy of the plant-based ointment containing 5 x MIC or 10 x MIC α-Pi, alone (2.5% and 5%, respectively), and 2% mupirocin, as a control, was assessed (Fig.2B). In the second experiment, a combinatorial mixture of α-Pi plus mupirocin at subinhibitory concentrations was compared, with both agents applied separately (Fig.2C).

We found that 5% v/v α-Pi decreased the viable cells per wound by 3-log compared to what occurred in the vehicle-treated wounds (Fig.2B). Mupirocin at 2%, as expected, also showed a bactericidal effect. When statistical analyses were performed by ANOVA with the Kruskal–Wallis test, no significant differences were observed between the CFU recovered after treatment with the ointment containing 5% α-Pi and those recovered after the treatment with commercial mupirocin 2% cream.

Subsequently, an ointment containing 2.5 x MIC α-Pi (1.25% v/v) plus 0.5% mupirocin was challenged, and its efficacy was compared to that of each compound, separately (Fig.2C). This combination revealed clear bactericidal activity against MRSA, with a nearly 4- to 5- log decrease in the number of CFU per wound compared to the

**Figure 2**. Timeline of the MRSA skin infection design (A). Survival of MRSA after treatment with 5 x minimum inhibitory concentrations (MIC) or 10 x MIC α-Pi-based ointment or 2% MUP alone (B) and 2.5 x MIC α-Pi plus 0.5% MUP (C). Number of colony-forming units (CFU) per wound area recovered from each animal; horizontal bars represent the median value of the CFU per wound of 3 independent experiments. α-Pi =α-pinene; MUP=mupirocin; CFU =colony-forming units.

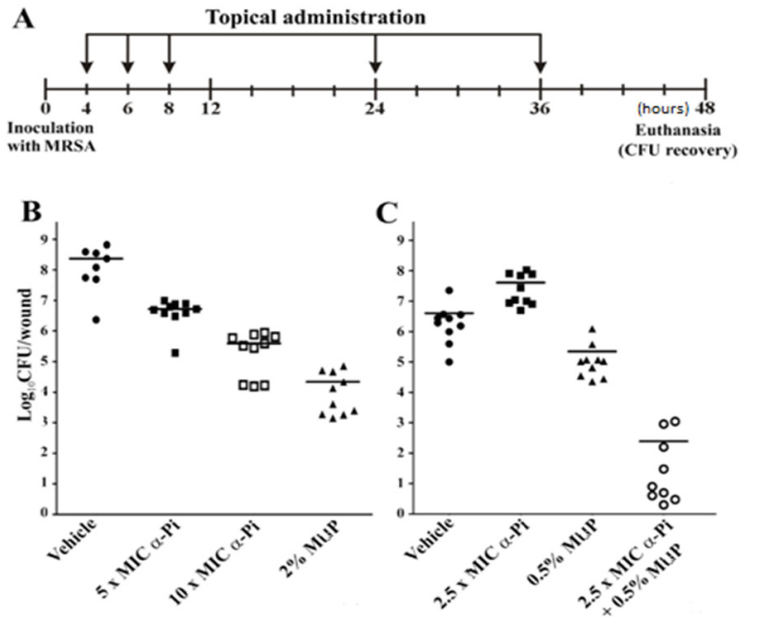
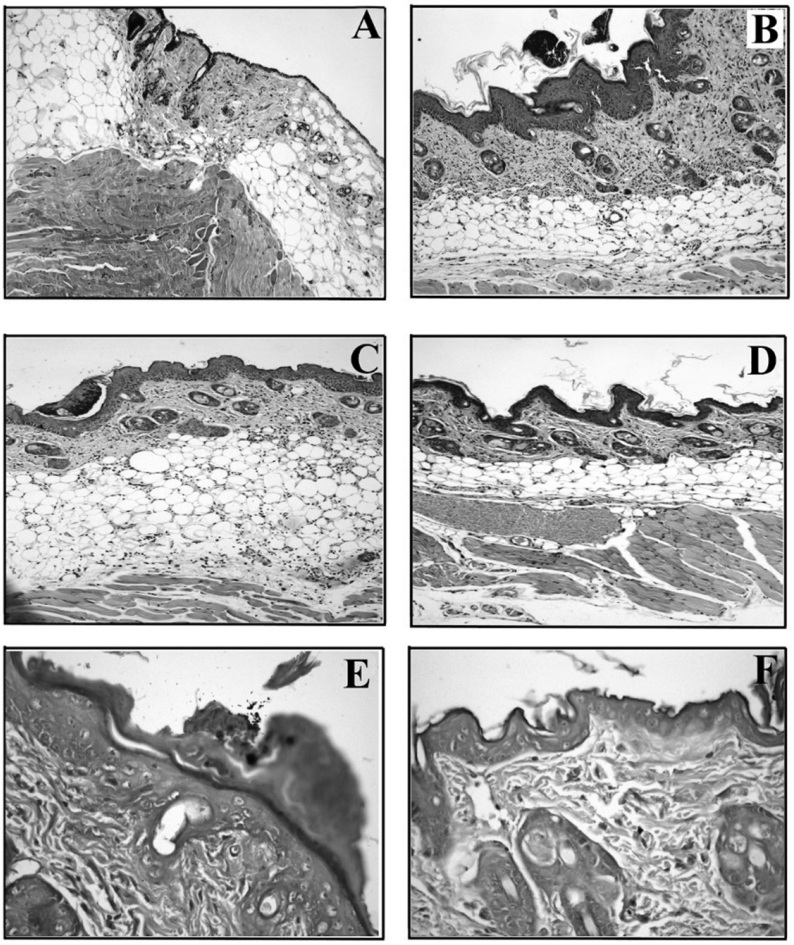


**Figure 3**. Representative images of histological analysis of mouse skin sections after hematoxylin and eosin (A-D, magnification X100) and Brown and Brenn staining (E and F, magnification X400). Skin without treatment (A) and treated with the vehicle (B and E), 2% mupirocin (C), or 10 x MIC α-pinene-based ointment (D and F). Bacteria were observed in the horny layer of the epidermis after treatment with the vehicle (E).




biopsies and severe inflammation in 1 appeared. In addition, 3 of the 4 specimens showed minimal bacteria in the horny layer, and the remaining specimen did not have any microorganisms (representative sample, Fig.3C). Interestingly, the 4 specimens treated with α-Pi at a concentration of 10 x MIC showed mild mixed inflammation in the dermis and hypodermis (Fig.3D): 2 without bacteria, 1 with isolated microorganisms, and only 1 with bacteria grouped in the horny layer (Fig.3F). Thus, the specimens treated with the plant compound showed a greater bacterial clearance with less inflammation than did those treated with the vehicle.

A dermal irritation test was performed on the rabbit skin to investigate the possible skin irritation responses of the formulation containing 2.5 x MIC α-Pi (1.25% v/v) plus 0.5% mupirocin (Fig. 4). After 72 h, the skin treated with either the vehicle (1% Tween 80 and 5% ethanol) or with the mixture containing both antimicrobials (compared to the skin that was untreated) displayed no signs of redness or erythema (Fig.4, upper panel). Accordingly, ultrasonographic evaluations of the skin thicknesses of the animals treated with 2.5 x MIC α-Pi plus 0.5% mupirocin-based ointment and of the thicknesses of the vehicle-treated and untreated skin did not evidence any statistically significant differences, using the Kruskal–Wallis test (1.63±0.18 mm; 1.81±0.32 mm; and 1.75±0.30 mm, respectively).

## Discussion

Our findings show that α-Pi at a quarter of its MIC (0.5% v/v) potentiated the bactericidal activity of mupirocin in a synergistic fashion. As a result, combinatory mixtures caused a 33-fold reduction of the MBC of the topical antibiotic when it was used against strains of multidrug-resistant MRSA. The plant compound also exhibited good performance in the in vivo clearance of the superficial MRSA infection from the skin, either alone or combined with mupirocin, after 5 topical applications, within 36 hours, post-infection. Therefore, our study shows for the first time that the pure plant compound inhibited the viability of MRSA and enhanced mupirocin activity *in vitro* and *in vivo*.

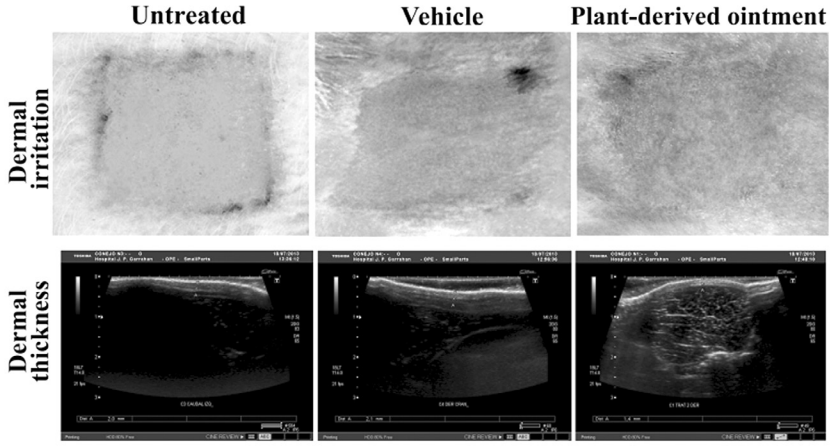
The identification of new molecules that may function synergistically with antibiotics as adjuvants is currently an important goal of research. Moreover, other authors have also reported on the enhancement of mupirocin-based antibacterial ointments by common antibiotics, such as neomycin sulfate (15).

Regarding the antibacterial activity of α-Pi, it was reported that at 62.5 to 125 mg/l (approximately 6%–12% v/v), the compound exhibited a microbicidal effect against the Gram-negative bacterium *Campylobacter jejuni* through membrane disruption and the inhibition of the efflux system, both of which being possible underlying mechanisms of action of this monoterpene (16).

Anti-bacterial agents against MRSA have previously been reported on; however, neither their toxicity nor their potential adverse effects have been tested to any great degree. This lack of information greatly limits the development of new formulations based on natural products. Nevertheless, the results of our toxicological analysis showed that the experimental formula containing a plant monoterpene had only limited side effects (17). The inflammatory response that occurred after establishing the MRSA infection was similar to that observed by Kugelberg et al (12).

The emergence of MRSA strains is a major threat and has serious implications for the epidemiology and treatment of *S. aureus* infections (18). In this regard, this α-Pi–based ointment may be useful in the development of innovative topical antibacterial formulations, as it proved to be both

**Figure 4**. Representative images of the response of skin irritation (upper panel) and dermal thickness in the rabbit skin, with the latter evaluated by ultrasonography (lower panel) after treatment with 2.5 x MIC α-pinene plus 0.5% mupirocin-based ointment compared to vehicle-treated and untreated skin after 72h.




safe and effective in terms of allowing the reduction of the mupirocin dose. Thus, the combination of α-Pi and mupirocin showed clinically relevant antimicrobial activity against MRSA infections, having a direct impact on health areas involved in the prophylaxis and treatment of staphylococcal infections.

## Resumen

Objetivo: El aumento del uso de mupirocina provoca resistencia a la misma, y se asocia con la persistencia de portadores de *Staphylococcus aureus* meticilino resistente (SAMR), hospitalización prolongada y carga económica sanitaria significativa. El objetivo de este estudio fue investigar la actividad antimicrobiana de compuestos de *Salvia rosmarinus* L. ("romero", antes *Rosmarinus officinalis*), solos o en combinación con mupirocina, contra SAMR multirresistentes de pacientes pediátricos reales. Métodos: La actividad antibacteriana *in vitro* del constituyente del aceite esencial del romero α-pineno (α-Pi), solo o combinado con mupirocina, fue evaluada para determinar la concentración inhibitoria mínima/bactericida mínima y los índices de concentración inhibitoria/bactericida fraccionaria contra cepas clínicas multirresistentes de SAMR. Se determinó la eficacia *in vivo* del α-Pi, solo o combinado con mupirocina, para erradicar la infección en un modelo optimizado de ratón con lesiones infectadas por SAMR. También se testeó toxicidad en biopsias de piel de ratón e irritación en piel de conejo. Resultados: α-pineno fue activo contra las cepas MRSA, mostrando sinergismo bactericida con mupirocina, *in vitro* e *in vivo*. Esta combinación mostró valores de CIF entre 0.2 y 0.4, reduciendo notablemente (33 veces) el CBM de la mupirocina. Una formulación tópica conteniendo α-Pi y mupirocina mejoró, *in vivo*, la eficacia de la mupirocina en modelo de piel de ratón con SAMR, en principio sin toxicidad significativa en piel de ratones y conejos. Conclusiones: Combinar mupirocina y α-Pi en una formulación tópica podría ser útil como innovación aplicable al tratamiento de infecciones por SAMR.

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