Open camera or QR reader and
scan code to access this article
and other resources online.

Blue Light Improves Antimicrobial Efficiency of Silver Sulfadiazine Via Catalase Inactivation

Sebastian Jusuf[1] and Ji-Xin Cheng, PhD[1,2]

Abstract

Background: Blue light exhibits the ability to deactivate catalase present in pathogens, significantly improving the antimicrobial performance of compounds such as hydrogen peroxide (H_2O_2). However, H_2O_2 is not used within clinical settings due to its short half-life, limiting its potential applications. In this study, we explore the usage of Food and Drug Administration-approved and clinically used silver sulfadiazine (SSD) as a potential alternative to H_2O_2, acting as a reactive oxygen species (ROS)-producing agent capable of synergizing with blue light exposure.
Materials and methods: For *in vitro* studies, bacterial strains were exposed to a continuous wave 405 nm light-emitting diode (LED) followed by treatment with SSD for varying incubation times. For *in vivo* studies, bacteria-infected murine abrasion wounds were treated with daily treatments of 405 nm LED light and 1% SSD cream for up to 4 days. The surviving bacterial population was quantified through agar plating and colony-forming unit quantification.
Results: Through a checkerboard assay, blue light and SSD demonstrated synergistic interactions. Against both gram-negative and gram-positive pathogens, blue light significantly improved the antimicrobial response of SSD within both phosphate-buffered saline and nutrient-rich conditions. Examination into the mechanisms reveals that the neutralization of catalase significantly improves the ROS-producing capabilities of SSD at the exterior of the bacterial cell, producing greater amounts of toxic ROS capable of exerting antimicrobial activity against the pathogen. Additional experiments reveal that the incorporation of light improves the antimicrobial performance of SSD within methicillin-resistant *Staphylococcus aureus* (MRSA)- and *Pseudomonas aeruginosa* strain 1 (PAO-1)-infected murine abrasion wounds.
Conclusions: As an established, clinically used antibiotic, SSD can act as a suitable alternative to H_2O_2 in synergizing with catalase-deactivating blue light, allowing for better translation of this technology to more clinical settings and further implementation of this treatment to more complex animal models.

Keywords: phototherapy, catalase, silver sulfadiazine, infectious diseases

Introduction

IN RECENT DECADES, the proliferation of antibiotic resistance has emerged as a ticking time bomb within the health care community. Due to agricultural and medical overuse, as well as slowing drug development, antibiotic resistance has developed within a wide array of bacterial strains.[1–3] The spread of resistance is estimated to not only increase the mortality of infections but also induce severe economic stress, increasing yearly global health care costs from $300 billion to more than $1 trillion by 2050.[4–6] Given these concerns, there is a need to develop alternative methods to treat infections.

In the past few years, blue light phototherapy has emerged as an exciting alternative to antibiotics due to its strong antimicrobial capabilities against a wide variety of pathogens.[7–9] Recent studies exploring the mechanisms of blue light phototherapy have found that 405–410 nm light induces

---

[1]Department of Biomedical Engineering, Boston University, Boston, Massachusetts, USA.
[2]Photonics Center, Boston University, Boston, Massachusetts, USA.

the structural deactivation of catalase within both bacterial and fungal species.[10,11] Catalase, a commonly expressed antioxidant enzyme found in aerobic organisms, is responsible for converting the toxic reactive oxygen species (ROS) hydrogen peroxide (H_2O_2) to water and oxygen.[12] Combining blue light with H_2O_2 was found to significantly improve the antimicrobial effectiveness of H_2O_2 against pathogens in both *in vitro* and *in vivo* conditions. Despite this, H_2O_2 usage remains problematic, as H_2O_2 is not utilized in clinical settings due to its extremely short half-life and high potential oxygen production, rendering it unsuitable for long-term treatments.[13–15] Given these concerns, alternatives to H_2O_2 are needed for potential clinical translation.

The antibiotic silver sulfadiazine (SSD) has emerged as an ideal alternative to H_2O_2 for synergy with blue light. As a Food and Drug Administration-approved antibiotic, SSD is most often used for the treatment of infected burns and wounds.[16–18] SSD exerts its mechanism of action partly through the binding of silver ions to amino, carboxyl, phosphate, imidazole, and thiol groups in proteins, triggering protein denaturation and inactivation.[19,20]

However, this binding is believed to indirectly cause intracellular ROS generation by disrupting proteins within the bacterial respiratory chain.[21] This ROS-generating capability, alongside its clinical usage, makes SSD an ideal compound to synergize with catalase deactivation. This theoretical synergy can also potentially improve the overall efficiency of the drug, helping minimize side effects such as inhibited wound healing by improving bioburden clearance and reducing the SSD application duration.[22–24] Thus, we hypothesize that light-induced catalase deactivation can improve the efficiency of SSD within both *in vitro* and *in vivo* environments.

Materials and Methods

Blue light source

Blue light was applied through a continuous wave 405 nm light-emitting diode (LED) (M405L4; Thorlabs) focused through a collimation adapter (SM2F32-A; Thorlabs). This application of 405 nm light will henceforth be referred to as CW-405. The CW-405 light beam was adjusted to obtain an illumination zone of $1\,cm^2$. Fluence was controlled via a T-Cube LED Driver (LEDD1B; Thorlabs) and applied at a constant $200\,mW/cm^2$.

Bacterial strains

Wild-type *Escherichia coli BW25113* and its catalase negative mutant *E. coli ΔkatGE* were obtained through Dr. Xilin Zhao of Rutgers University in New Brunswick, New Jersey, USA. Methicillin-resistant *Staphylococcus aureus* (MRSA) (USA300) and *Pseudomonas aeruginosa* strain 1 (PAO-1) (ATCC 47085) were obtained through Dr. Mohamed N. Seleem of Virginia Tech University in Blacksburg, Virginia, USA.

SSD preparation

For *in vitro* studies, SSD salt (481181; Sigma–Aldrich) was dissolved in diluted (0.7–1.4%) ammonium hydroxide (NH_4OH) (L13168; Alfa Aesar). For *in vivo* studies, topical 1% SSD cream (67877012450; Ascend) was used.

In vitro *blue light catalase deactivation and SSD treatment*

Bacterial strains were cultured overnight in tryptic soy broth (TSB) to stationary phase. The next day, bacteria was resuspended and diluted in $1\times$ phosphate-buffered saline (PBS) to an OD600 of 1.0. For light treatment, bacterial aliquots were placed on a coverslip and exposed to $200\,mW/cm^2$ of CW-405. For a checkerboard assay, $2\,\mu L$ droplets were treated for 0, 2.5, 5, 10, 20, and 40 min, diluted in 2 mL of TSB, and plated in a 96-well plate. Following this, SSD was diluted twofold from a concentration of $64\,\mu g/mL$ to concentrations of 32, 16, 8, and $4\,\mu g/mL$. The assay was incubated at 37°C for 48 h before the OD600 was measured with a plate reader to identify the minimal inhibitory concentration (MIC) of CW-405 and SSD alone and in combination. Synergistic interactions were determined by calculating the fractional inhibitory concentration index (FICI) defined by the following equation:[25]

$$\frac{MIC_A^{Comb}}{MIC_A^{Alone}} + \frac{MIC_B^{Comb}}{MIC_B^{Alone}} = FIC_A + FIC_B = FICI.$$

MIC^{Alone} refers to the MIC of isolated agents while MIC^{Comb} corresponds to the MIC of agents in combination. For colony-forming unit (CFU) studies, $10\,\mu L$ aliquots were treated for 5 min ($60\,J/cm^2$). Once complete, the aliquot was removed and diluted within $990\,\mu L$ of either PBS or TSB. Varying concentrations of SSD dissolved in around 1% of NH_4OH were then added to each dilution. To account for the NH_4OH within the SSD solution, equal amounts of low concentration NH_4OH were added to non-SSD-treated dilutions as well. Following the addition of SSD, samples were incubated for up to 2 h within a 37°C incubator at an RPM of 200. Once finished, samples were serially diluted and plated onto tryptic soy agar plates. The resulting CFU was then quantified.

Catalase rescue and salvaging

Overnight cultured PAO-1 and MRSA were subjected to light treatment as described previously. Following treatment, $100\,\mu L$ of 1 mg/mL bovine catalase (C9322; Sigma–Aldrich) was added to $900\,\mu L$ of each suspension, adding 200–500 U of catalase to each solution. Next, $2\,\mu g/mL$ of SSD was added. The suspensions were incubated for 1 h at 37°C, plated, and quantified.

ROS detection and quantification

ROS production was quantified through a hydroxyl radical and peroxynitrite sensor (HPF) dye (H36004; Thermo Fisher Scientific). Overnight cultured PAO-1 and MRSA were treated to $60\,J/cm^2$ of CW-405 and $2\,\mu g/mL$ of SSD in the process as described previously. Following SSD addition, $2\,\mu M$ of HPF was added and suspensions were incubated for 30 min at 37°C. Once complete, $100\,\mu L$ of suspension was transferred to a 96-well plate and fluorescence ($n=3$) was quantified at an excitation/emission setting of 490/515 nm. Background fluorescence was quantified by adding $2\,\mu M$ of HPF to PBS and incubating the solution in 37°C for 30 min. Measured fluorescence was normalized by subtracting the background fluorescence.

In vivo *murine model*

Murine abrasion wounds were generated following the procedure established by Dong et al.[10] Seven- to eight-week-old BALB/c female mice (000651; Jackson Laboratory) were dorsally shaved and placed under isoflurane anesthesia. 1 cm² abrasion wounds were created by a No. 15 sterile scalpel. A 10 μL aliquot containing 10^6 CFU of log phase MRSA or 10^8 CFU of log phase PAO-1 was applied to the surface of each wound. Treatment began 2 h after infection. For each bacteria tested, mice were separated into four groups: untreated, light only, SSD only, and combination. Light treatment consisted of two 60 J/cm² CW-405 treatments applied onto wounds with 5-min breaks between treatments. A single light session would consist of 120 J/cm² of exposure. For SSD treatment, 1% SSD cream was applied directly to the wound surface. In the combination treatment groups, mice would receive light treatment followed immediately by SSD cream application.

For the MRSA wounds, the untreated, SSD only, and combination groups consisted of $n = 7$ wounds, whereas the light only group consisted of $n = 5$ wounds. The MRSA groups were treated daily over 4 days for a total light dosage of 480 J/cm². Twenty-four hours after the last treatment, MRSA-infected mice were euthanized and the wounds were extracted, homogenized in 2 mL of PBS, and plated on *Staphylococcus aureus* selective mannitol agar plates. For the PAO-1 model, each group consisted of $n = 4$ wounds. The PAO-1 groups were treated twice in the span of 24 h, with 12-h breaks between sessions, totaling to a final dosage of 240 J/cm². Four hours after the last treatment, PAO-1-infected mice were euthanized and wounds were removed, homogenized, and plated on *P. aeruginosa* selective cetrimide agar plates. The resulting CFU was then quantified.

Statistical analysis

Student unpaired *t*-tests were used to conduct statistical analysis via GraphPad PRISM version 9.0.0. Significance (*) was set at *p*-values <0.05.

Study approval

Murine infected abrasion models were approved under protocol PROTO201800535 by the Institutional Animal Care and Use Committee (IACUC) at Boston University.

Results

Blue light and SSD exhibit synergistic response

To confirm synergy between blue light and SSD, a checkerboard assay was performed on the model bacteria *E. coli* BW25113 to identify the FICI in TSB (Fig. 1a). The FICI can be used to determine the type of interactions between two agents, with synergistic interactions identified though FICI values ≤0.5.[26] *E. coli* was found to exhibit an MIC of 480 J/cm² for CW-405 and 32 μg/mL for SSD. In contrast, the MICs of the agents in combination were found to be 60 J/cm² for CW-405 and 8 μg/mL for SSD. Based on the FICI equation listed, these values correspond to an FICI of 0.375, confirming the presence of synergy. To further explore the capability of light to improve SSD performance, the CFU of *E. coli* after light and SSD treatment was evaluated. Following 1 h of incubation in PBS, both
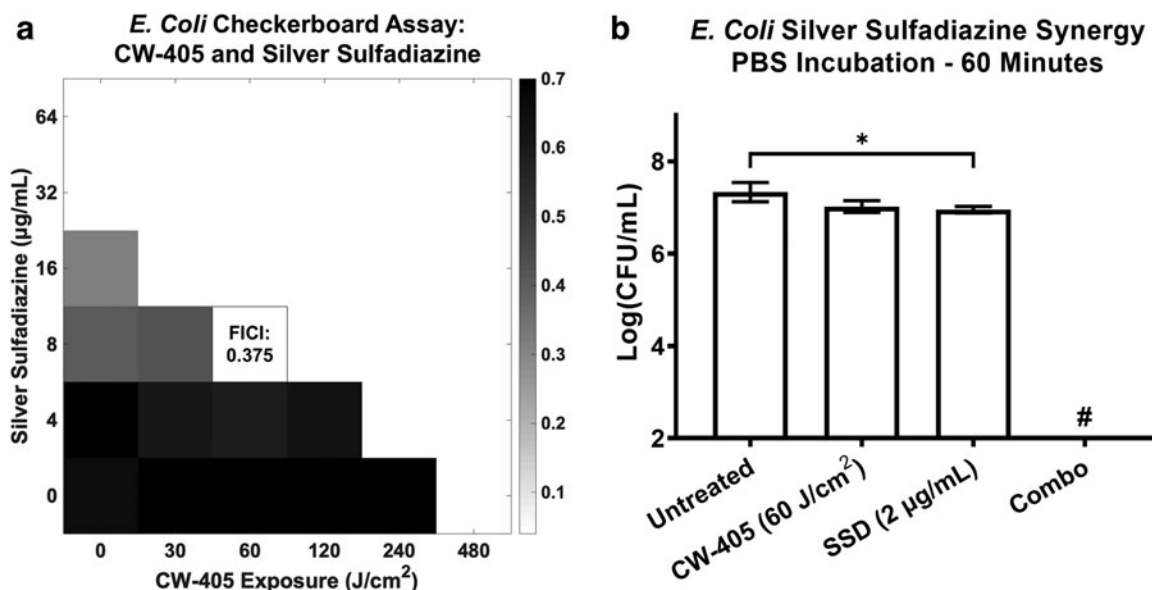

FIG. 1. Combination of catalase-deactivating CW-405 and SSD results in synergistic interactions within model bacteria organism *Escherichia coli* BW25113. **(a)** Checkerboard assay of *E. coli* exposed to varying dosages of CW-405 and SSD within TSB. Treatment with 60 J/cm² of CW-405 and 8 μg/mL SSD results in an FICI of 0.375. FICI values less than 0.5 indicate synergistic interactions. **(b)** CFU measurements of bacterial population indicate combination of light and SSD resulted in complete eradication, further confirming the synergistic interactions. In contrast, light or SSD alone has little impact on the overall CFU. *p < 0.05, #below detection limit. CFU, colony-forming unit; FICI, fractional inhibitory concentration index; SSD, silver sulfadiazine; TSB, tryptic soy broth.

60 J/cm^2 light and 2 μg/mL SSD reduced the CFU of *E. coli* by less than 0.5 log. In contrast, the combination treatment completely eradicated the *E. coli* population beyond the detection limit (Fig. 1b).

Next, the treatment was evaluated on gram-negative *P. aeruginosa* (PAO-1) and gram-positive MRSA. PAO-1 treated to either CW-405 or SSD (2 μg/mL) experienced a less than 0.5 log CFU reduction, whereas the combination-treated samples experienced complete eradication (Fig. 2a). MRSA treated to either CW-405 or SSD (5 μg/mL) resulted in a 0.5 log CFU reduction, whereas the combination treatment also demonstrated full eradication (Fig. 2b).

Within more nutrient-rich environments, the combination treatment conducted on bacteria incubated within TSB for 2 h was found to require higher SSD concentrations to achieve an improved response. For PAO-1, CW-405 alone induced a 1 log CFU reduction, whereas treatment with 20 μg/mL of SSD induced a 0.5 log reduction. The combination treatment of PAO-1 resulted in a 3 log CFU reduction (Fig. 2c). For MRSA, treatment with CW-405 and 50 μg/mL of SSD resulted in a 1 and 0.5 log CFU reduction, respectively, identical to the PAO-1 results. However, the combination treatment of MRSA was slightly more effective with a log CFU reduction of 4 (Fig. 2d).
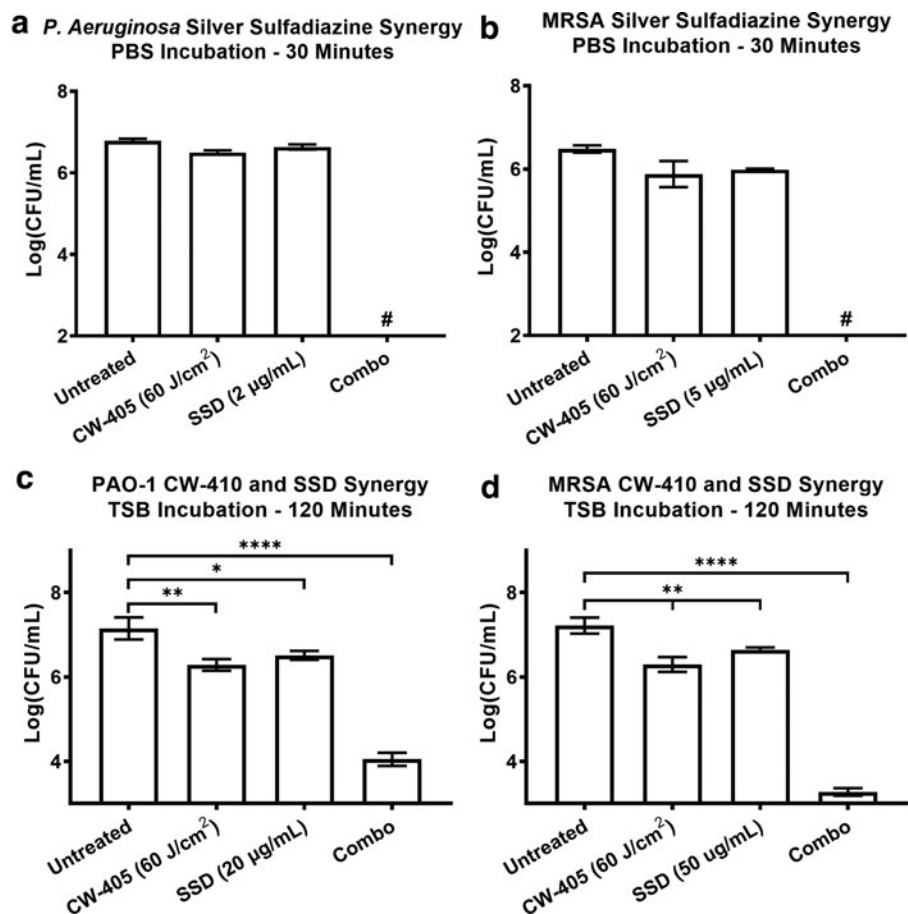
Mechanisms of blue light and SSD synergy

To investigate the mechanisms behind light and SSD synergy, the role of catalase against SSD activity was explored. In wild-type *E. coli*, combination treatments of CW-405 and SSD (1 μg/mL) induced a 1 log CFU reduction compared with the light-treated samples (Fig. 3a). However, the same treatment applied to the catalase-negative mutant *E. coli ΔkatGE* resulted in no significant differences between the light-treated mutant and the combination-treated mutant (Fig. 3b). Additional experiments revealed that the addition of exogenous catalase completely neutralized the effectiveness of the combination treatment in both PAO-1 and MRSA. For PAO-1, the combination treatment alone resulted in the complete eradication of PAO-1, whereas the addition of catalase was found to slightly increase the CFU by less than 0.5 log (Fig. 3c).

For MRSA, while the combination treatment alone resulted in a 2 log CFU reduction, the addition of catalase resulted in no differences between the light- and combination-treated samples (Fig. 3d). These results indicate that increased ROS presence contributes to the increased antimicrobial activity of SSD, which exogenous catalase can neutralize. To confirm this, ROS levels were measured through an ROS-detecting HPF dye. In PAO-1, individual treatments of CW-405 and SSD increased HPF fluorescence by a factor of 13.7 and 3.4, respectively. In comparison, the combination treatment increased fluorescence by a factor of 27.7 (Fig. 3e). For MRSA, both CW-405 and SSD individually increased fluorescence by a factor of 1.5, whereas the combination treatment increased fluorescence by a factor of 4.6 (Fig. 3f).

FIG. 2. CFU measurements of CW-405 (60 J/cm^2)-treated **(a)** *Pseudomonas aeruginosa* (PAO-1), and **(b)** MRSA following incubation with SSD in PBS. Light or SSD alone has little impact on overall CFU, whereas the combination of the two agents results in complete eradication. In nutrient-rich conditions, CFU measurements of CW-405 (60 J/cm^2)-treated **(c)** *P. aeruginosa* (PAO-1), and **(d)** MRSA following incubation with SSD in TSB indicate that while higher dosages of SSD are required, improved performance with CW-405 still occurs. ****$p < 0.0001$, **$p < 0.01$, *$p < 0.05$, #below detection limit. MRSA, methicillin-resistant *Staphylococcus aureus*; PAO-1, *Pseudomonas aeruginosa* strain 1; PBS, phosphate-buffered saline.
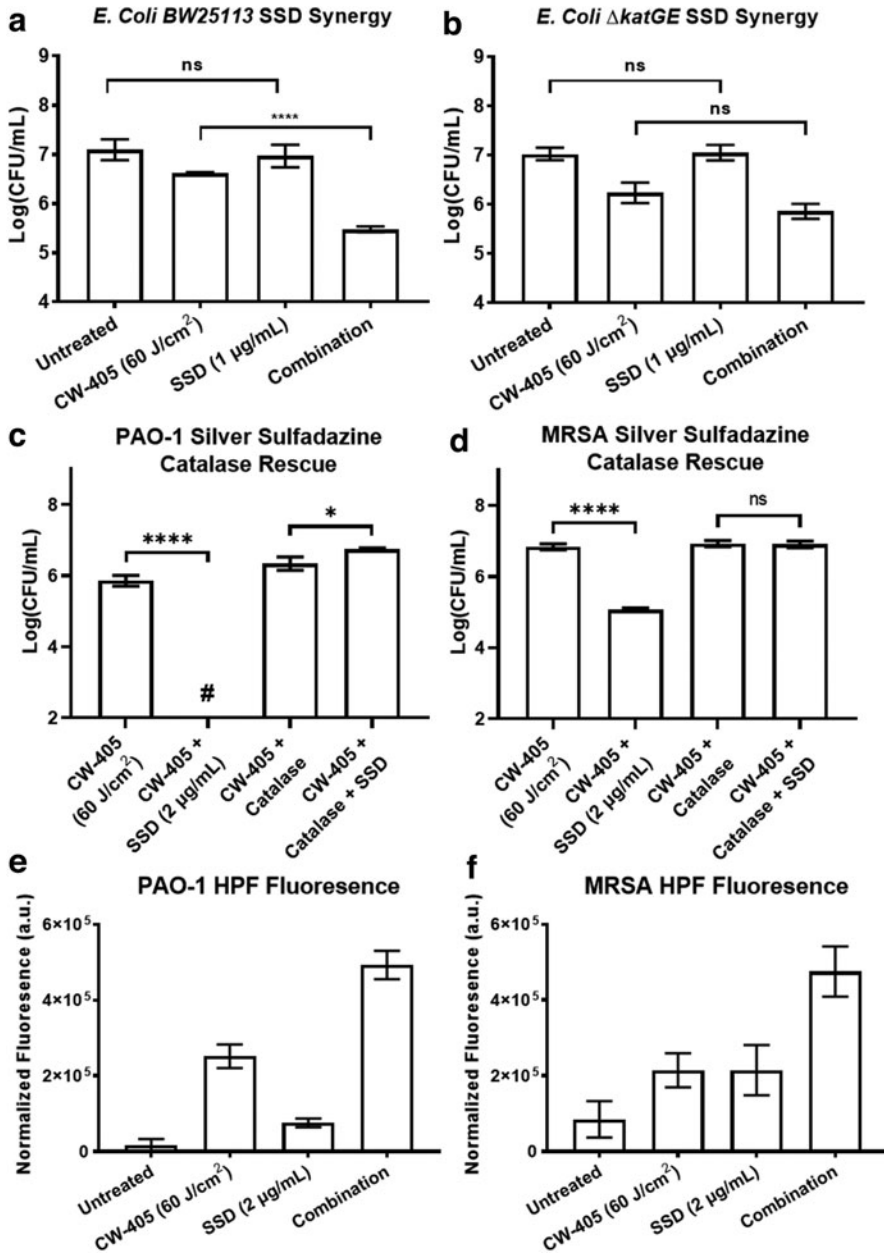
FIG. 3. Mechanisms of CW-405 and SSD synergy. The combination of CW-405 ($60 \, J/cm^2$) and low concentration SSD results in **(a)** a 1 log reduction in wild-type *Escherichia coli* but **(b)** no significant reduction in catalase-negative *E. coli* *ΔkatGE* mutants. Further investigation in the possible role of catalase in the synergy reveals that the addition of exogenous bovine catalase completely neutralizes the synergistic effects of CW-405 and SSD in both **(c)** PAO-1 and **(d)** MRSA. The impact of catalase deactivation on the ROS production of SSD was further explored through an ROS-detecting HPF dye. When applying the combination treatment to **(e)** PAO-1 and **(f)** MRSA, HPF dye reveals significant increases in ROS fluorescence for the combination-treated samples. ****$p < 0.0001$, *$p < 0.05$, ns, no significance, #below detection limit. HPF, hydroxyl radical and peroxynitrite sensor; ROS, reactive oxygen species.

In vivo *murine model*

A murine infected abrasion model was used to determine the effectiveness of blue light and SSD within *in vivo* conditions. Infected wounds (Fig. 4a) were fully covered with SSD to maximize exposure (Fig. 4b). CFU counts of MRSA wounds (Fig. 4c) indicate that while the light treatment alone had no significant effect on the bioburden of the MRSA wounds, SSD-treated MRSA wounds saw a near fourfold increase in bioburden. Despite this, the combination treatment resulted in an 85% decrease in MRSA bioburden (Fig. 4d). For PAO-1-infected wounds, CFU measurements (Fig. 4e) indicated that individual CW-405 or SSD treatment had no significant effect on the bioburden. Combination-treated wounds, however, experienced a 98% reduction in CFU bioburden, constituting a significant improvement in effectiveness (Fig. 4f).

Discussion

Based on their FICI, the combination of catalase-deactivating blue light and SSD exhibited strong synergistic interactions. The effectiveness of this treatment was further validated by the complete eradication of multiple bacterial strains within PBS upon treatment with both light and low dosage SSD. In comparison, the individual treatments of light or SSD exerted minimal impact on the bacteria, at most exerting a CFU log reduction of 0.5. These observed interactions between CW-405 and SSD behaved identically to the synergy observed between light and H_2O_2, indicating that SSD can act as a viable alternative to H_2O_2.[10]

Like H_2O_2, catalase deactivation allowed for bacterial eradication through SSD at sub-MIC concentrations, with *P. aeruginosa* reported to have an MIC range of 16–32 $\mu g/mL$ while MRSA strains have a range of 64–128 $\mu g/mL$.[27]

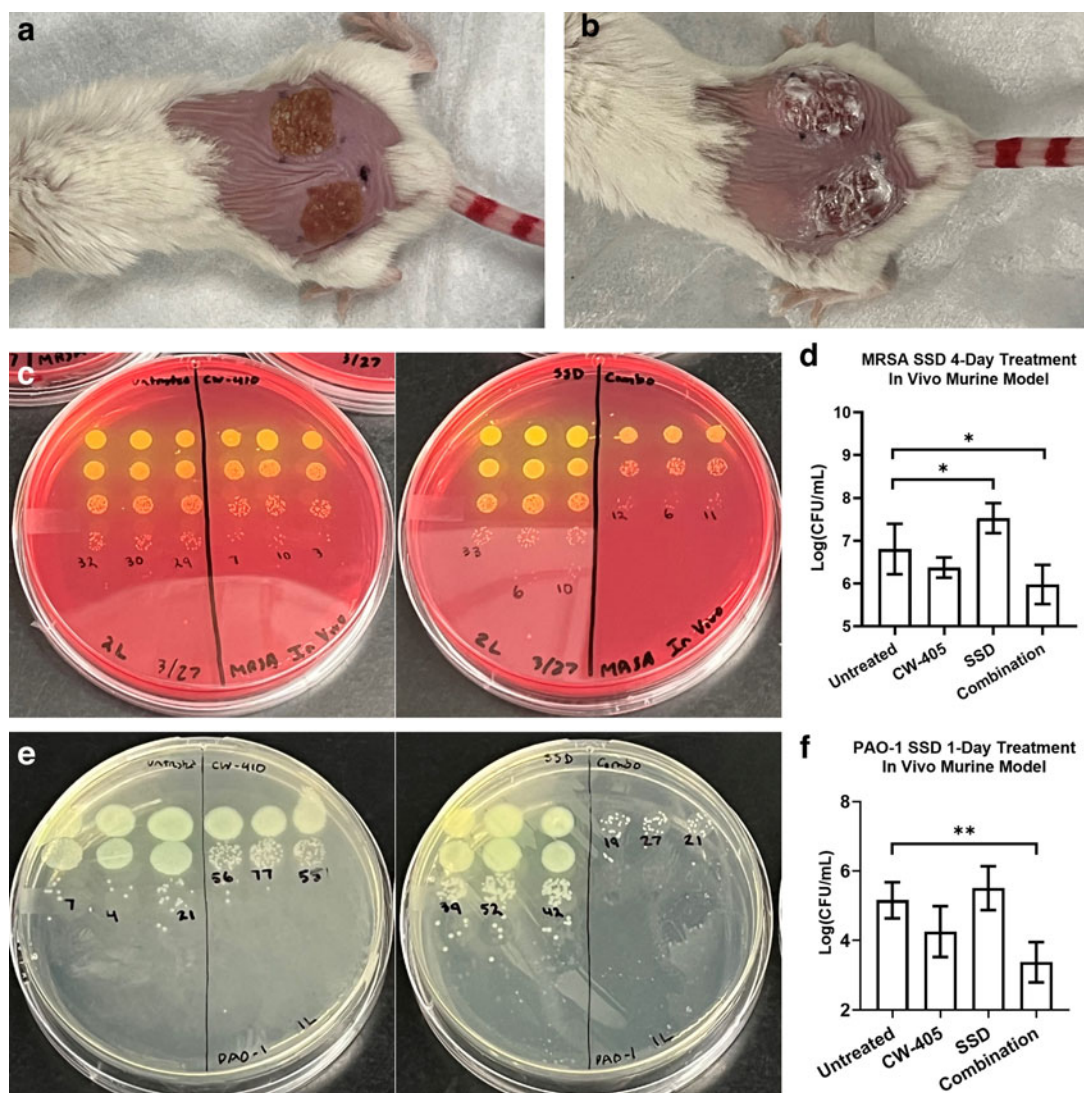**FIG. 4.** MRSA- and PAO-1-infected murine abrasion wound models were used to evaluate the effectiveness of blue light and SSD combination treatment. **(a)** $1\,cm^2$ abrasion wounds were generated on the dorsal flanks of BALB/c mice and infected with bacterial loads. **(b)** When applying 1% SSD cream to infected wounds, it was ensured that the wound would be covered by the SSD cream. MRSA-infected wounds treated with daily application sessions of CW-405 ($120\,J/cm^2$) and 1% SSD cream for 4 days were **(c)** quantified via CFU plating on mannitol salt agar and **(d)** found to exhibit minor average improvement from the combination treatment in comparison to the untreated wounds. In PAO-1-infected wounds, wounds treated with CW-405 ($120\,J/cm^2$) and SSD cream twice in 24 h and **(e)** plated on cetrimide agar were **(f)** found to improve the efficacy of PAO-1 significantly, with a near 2 log reduction in CFU population observed from the untreated group. In both murine models, SSD alone was found to be either ineffective in the case of PAO-1-infected wounds or beneficial to bacterial growth in the case of MRSA-infected wounds. $**p < 0.01$, $*p < 0.05$.

Even within nutrient-rich environments, the improved efficiency of SSD by CW-405 was found to remain, although requiring higher concentrations of SSD. The greater SSD dosage needed to achieve improved efficiency can be attributed to the active metabolism of bacteria within the media, as exposure to sublethal ROS sources would trigger the overexpression of oxidative stress defense genes in response.[28–30] Despite this, CW-405 incorporation significantly improves the performance of SSD by 3–4 log compared with the antibiotic alone.

The fact that light had no impact on the SSD activity in catalase-negative *E. coli* mutants indicates that it is the specific removal of catalase that contributes to the synergy between light and SSD. This is supported by the complete neutralization of the combination treatment observed by the addition of exogenous bovine catalase, which not only demonstrates the importance catalase plays as a defense mechanism against SSD but also indicates that the intracellular ROS produced indirectly by SSD can diffuse out of the cell into the exterior environment.[21]

Without catalase presence, the intracellular ROS produced by light- and SSD-treated cells are likely increasing ROS levels within the bacterial environment, further propagating oxidative damage to surrounding cells. This increased ROS concentration caused by catalase removal is supported by the higher ROS levels detected within

combination-treated bacteria. For PAO-1 and MRSA, the combination treatment fluorescence increased 62% and 53% over the added individual fluorescence of CW-405 and SSD, respectively. The increased ROS availability caused by the absence of catalase would provide more opportunities for the ROS to exert their antimicrobial activity on the cell, therefore increasing the efficiency of SSD following exposure to light.

Interestingly, the MRSA HPF fluorescence was found to be significantly lower than the PAO-1 fluorescence. The lower fluorescence is likely caused by the presence of additional antioxidants such as the membrane-bound staphyloxanthin pigment in MRSA neutralizing the ROS before they can react with HPF.[31,32] This pigment also likely contributes to the higher SSD resistance observed in MRSA.

While light and SSD exhibited clear synergy within an *in vitro* environment, *in vivo* studies showed promising results as well. Combination treatment in both MRSA- and PAO-1-infected wounds significantly enhanced the antimicrobial activity of SSD and achieved significant bioburden reduction compared with their untreated counterparts. In contrast, individual light treatments did not significantly differentiate from untreated samples for both bacterial models. While SSD only treatment had no effect on PAO-1-infected wounds, MRSA wounds treated with SSD alone were observed to experience a 401.1% increase in bioburden. This increase in MRSA population can likely be attributed to a combination of factors, such as the tendency for mice to lick their own or other mice's back in response to cream application.[33] Such interference would significantly reduce the SSD concentration available on the wound and lead to subinhibitory dosages, resulting in potential growth driven by the hormetic effects of subinhibitory antibiotic concentrations.[34,35]

Regardless, infected wounds exhibited greater vulnerability to combination treatment, with PAO-1 infections demonstrating greater sensitivity to the treatment, achieving a near 2 log CFU reduction compared with the less than 1 log CFU reduction observed in MRSA. The sensitivity of PAO-1 to the combination treatment suggests that catalase deactivation may provide a way of resensitizing SSD-resistant *P. aeruginosa* to the drug, reviving the usage of the drug against previously resistant strains.[36,37] In addition, the increased effectiveness of SSD with light can allow for lower dosages and durations of SSD to be used against infected wounds, further minimizing potential side effects such as wound healing inhibition.[22] The effectiveness of this treatment can also provide a strong foundation for additional studies examining the effectiveness of this treatment on other types of infected wounds, such as chronic wounds or diabetic ulcers.[38,39]

Conclusions

Overall, by combining catalase-deactivating blue light with SSD, we have established a nondrug-reliant method of sensitizing pathogens to an established clinical antibiotic. The improved effectiveness of SSD with CW-405 was found within a broad spectrum of pathogens in both PBS and nutrient-rich conditions. Application of CW-405 and SSD was also found to be effective within *in vivo* environments, providing a foundation for the incorporation of light into

traditional treatments. By establishing SSD as a viable alternative to H_2O_2 in blue light synergy, we can provide a potential direction for the development of new antimicrobial agents that could be created to specifically synergize with light-induced catalase deactivation.

Authors' Contributions

S.J. and J.-X.C. conceived the idea of combining catalase deactivation with SSD. S.J. designed and conducted all experiments. J.-X.C. oversaw all experiments. S.J. and J-X.C. co-wrote the article.

Disclaimer

Author Disclosure Statement

Funding Information

References

1. Goldman E. Antibiotic abuse in animal agriculture: Exacerbating drug resistance in human pathogens. Hum Ecol Risk Assess 2004;10(1):121–134; doi: 10.1080/10807030490281016.

2. Shea KM. Antibiotic resistance: What is the impact of agricultural uses of antibiotics on children's health? Pediatrics 2003;112(1 Pt 2):253–258.

3. Ventola CL. The antibiotic resistance crisis: Part 1: Causes and threats. Pharm Therap 2015;40(4):277–283.

4. Graham CJ. The global threat of antibiotic resistance: What can be done? J Global Health Rep 2017;1:e2017002.

5. Yoshikawa TT. Antimicrobial resistance and aging: Beginning of the end of the antibiotic era? J Am Geriatr Soc 2002;50(7 Suppl):S226–S229; doi: 10.1046/j.1532-5415.50.7s.2.x.

6. Ahmad M, Khan AU. Global economic impact of antibiotic resistance: A review. J Glob Antimicrob Resist 2019;19: 313–316; doi: 10.1016/j.jgar.2019.05.024.

7. Leanse LG, Dos Anjos C, Mushtaq S, et al. Antimicrobial blue light: A 'Magic Bullet' for the 21st century and beyond? Adv Drug Deliv Rev 2022;180:114057; doi: 10.1016/j.addr.2021.114057.

8. Wang Y, Wang Y, Wang Y, et al. Antimicrobial blue light inactivation of pathogenic microbes: State of the art. Drug Resist Updat 2017;33–35:1–22; doi: 10.1016/j.drup.2017.10.002.

9. McDonagh AF. Phototherapy: From ancient Egypt to the new millennium. J Perinatol 2001;21 Suppl 1:S7–S12; doi: 10.1038/sj.jp.7210625.

10. Dong PT, Jusuf S, Hui J, et al. Photoinactivation of catalase sensitizes a wide range of bacteria to ROS-producing agents and immune cells. JCI Insight 2022;7(10):153079; doi: 10.1172/jci.insight.153079.

11. Dong PT, Zhan Y, Jusuf S, et al. Photoinactivation of catalase sensitizes Candida albicans and Candida auris to ROS-producing agents and immune cells. Adv Sci (Weinh) 2022;9(10):e2104384; doi: 10.1002/advs.202104384.

12. Aebi H. Catalase. In: Methods of Enzymatic Analysis (Second Edition). (Bergmeyer HU. ed.) Academic Press: Cambridge, MA; 1974; pp. 673–684.

13. Cambiaso-Daniel J, Boukovalas S, Bitz GH, et al. Topical antimicrobials in burn care: Part 1-topical antiseptics. Ann Plast Surg 2018; doi: 10.1097/SAP.0000000000001297.

14. Mut M, Yemisci M, Gursoy-Ozdemir Y, et al. Hydrogen peroxide-induced stroke: Elucidation of the mechanism in vivo. J Neurosurg 2009;110(1):94–100; doi: 10.3171/2008.3.17434.

15. Beattie C, Harry LE, Hamilton SA, et al. Cardiac arrest following hydrogen peroxide irrigation of a breast wound. J Plast Reconstr Aesthet Surg 2010;63(3):e253–e254; doi: 10.1016/j.bjps.2009.07.012.

16. Oaks RJ, Cindass R. Silver Sulfadiazine. StatPearls Publishing: Treasure Island, FL, USA; 2021.

17. Hoffmann S. Silver sulfadiazine: An antibacterial agent for topical use in burns. Scand J Plastic Reconstr Surg 1984; 18(1):119–126; doi: 10.3109/02844318409057413.

18. Carr HS, Wlodkowski TJ, Rosenkranz HS. Silver sulfadiazine: In vitro antibacterial activity. Antimicrob Agents Chemother 1973;4(5):585–587; doi: 10.1128/AAC.4.5.585.

19. Gordon O, Vig Slenters T, Brunetto PS, et al. Silver coordination polymers for prevention of implant infection: Thiol interaction, impact on respiratory chain enzymes, and hydroxyl radical induction. Antimicrob Agents Chemother 2010;54(10):4208–4218; doi: 10.1128/AAC.01830-09.

20. Fox CL, Jr., Modak SM. Mechanism of silver sulfadiazine action on burn wound infections. Antimicrob Agents Chemother 1974;5(6):582–588; doi: 10.1128/AAC.5.6.582.

21. Park HJ, Kim JY, Kim J, et al. Silver-ion-mediated reactive oxygen species generation affecting bactericidal activity. Water Res 2009;43(4):1027–1032; doi: 10.1016/j.watres.2008.12.002.

22. Cho Lee AR, Leem H, Lee J, et al. Reversal of silver sulfadiazine-impaired wound healing by epidermal growth factor. Biomaterials 2005;26(22):4670–4676; doi: 10.1016/j.biomaterials.2004.11.041.

23. Fuller FW. The side effects of silver sulfadiazine. J Burn Care Res 2009;30(3):464–470; doi: 10.1097/BCR.0b013e3181a28c9b.

24. Akhoondinasab MR, Akhoondinasab M, Saberi M. Comparison of healing effect of aloe vera extract and silver sulfadiazine in burn injuries in experimental rat model. World J Plast Surg 2014;3(1):29–34.

25. Botelho MG. Fractional inhibitory concentration index of combinations of antibacterial agents against cariogenic organisms. J Dent 2000;28(8):565–570; doi: 10.1016/s0300-5712(00)00039-7.

26. Odds FC. Synergy, antagonism, and what the chequerboard puts between them. J Antimicrob Chemother 2003;52(1):1; doi: 10.1093/jac/dkg301.

27. Hamilton-Miller JM, Shah S, Smith C. Silver sulphadiazine: A comprehensive in vitro reassessment. Chemotherapy 1993;39(6):405–409; doi: 10.1159/000238985.

28. Elkins JG, Hassett DJ, Stewart PS, et al. Protective role of catalase in Pseudomonas aeruginosa biofilm resistance to hydrogen peroxide. Appl Environ Microbiol 1999;65(10):4594–4600; doi: 10.1128/AEM.65.10.4594-4600.1999.

29. Storz G, Tartaglia LA, Farr SB, et al. Bacterial defenses against oxidative stress. Trends Genet 1990;6(11):363–368; doi: 10.1016/0168-9525(90)90278-e.

30. Martins D, English AM. Catalase activity is stimulated by H2O2 in rich culture medium and is required for H_2O_2 resistance and adaptation in yeast. Redox Biology 2014;2: 308–313; doi: 10.1016/j.redox.2013.12.019.

31. Liu GY, Essex A, Buchanan JT, et al. Staphylococcus aureus golden pigment impairs neutrophil killing and promotes virulence through its antioxidant activity. J Exp Med 2005;202(2):209–215; doi: 10.1084/jem.20050846.

32. Hall JW, Yang J, Guo H, et al. The Staphylococcus aureus AirSR two-component system mediates reactive oxygen species resistance via transcriptional regulation of staphyloxanthin production. Infect Immun 2017;85(2):e00838-16; doi: 10.1128/IAI.00838-16.

33. Berbudi A, Fadlillah AA, Afni M, et al. Effect of Curcuma longa crude extract, curcumin and nano curcumin-based gel topical administration on excised skin wound healing in Swiss-Webster Mice. Biomed Pharmacol J 2021;14(2): 635–641.

34. Davies J, Spiegelman GB, Yim G. The world of subinhibitory antibiotic concentrations. Curr Opin Microbiol 2006; 9(5):445–453; doi: 10.1016/j.mib.2006.08.006.

35. Iavicoli I, Fontana L, Agathokleous E, et al. Hormetic dose responses induced by antibiotics in bacteria: A phantom menace to be thoroughly evaluated to address the environmental risk and tackle the antibiotic resistance phenomenon. Sci Total Environ 2021;798:149255; doi: 10.1016/j.scitotenv.2021.149255.

36. Heggers JP, Robson MC. The emergence of silver sulphadiazine-resistant Pseudomonas aeruginosa. Burns 1978; 5(2):184–187; doi: 10.1016/S0305-4179(78)80043-6.

37. Pirnay JP, De Vos D, Cochez C, et al. Molecular epidemiology of Pseudomonas aeruginosa colonization in a burn unit: Persistence of a multidrug-resistant clone and a silver sulfadiazine-resistant clone. J Clin Microbiol 2003;41(3): 1192–1202; doi: 10.1128/JCM.41.3.1192-1202.2003.

38. Landis SJ. Chronic wound infection and antimicrobial use. Adv Skin Wound Care 2008;21(11):531–540; doi: 10.1097/01.ASW.0000323578.87700.a5.

39. Chang M, Nguyen TT. Strategy for treatment of infected diabetic foot ulcers. Acc Chem Res 2021;54(5):1080–1093; doi: 10.1021/acs.accounts.0c00864.

Address correspondence to:
Ji-Xin Cheng, PhD
Department of Biomedical Engineering
Boston University
8 St. Mary's St. Room 827
Boston, MA 02115
USA

E-mail: jxcheng@bu.edu