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Application of Riboflavin and Curcumin as Natural Photosensitizers for Antimicrobial Photodynamic Inactivation against *Staphylococcus aureus*: A Study for Skin Disease

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Abstract

Atopic Dermatitis (AD) and Actinic Keratosis (AK) are becoming increasingly prevalent in developing countries, including Indonesia. *Staphylococcus aureus*, a common microorganism associated with both conditions, presents treatment challenges due to the increasing antibiotic resistance and associated side effects. Photodynamic Inactivation (PDI), which employs natural photosensitizers such as riboflavin and curcumin in combination with Omega Light LED-a technology commonly used in aesthetic treatments-offers a potential alternative. In this study, riboflavin and curcumin were applied separately at a concentration of 0.015% (w/v) and irradiated with red (λ = 640 nm), blue (λ = 423 nm), or green (λ = 532 nm) light using an Omega Light LED device (O'melon). Cell viability was assessed using an ELISA reader at 595 nm after irradiation durations of 10, 30, and 60 minutes. Skin toxicity was predicted using Toxtree 3.1.0, Pred-Skin 3.0, and pkCSM web-based tools. Results showed that the photosensitizers without irradiation were not cytotoxic to *Staphylococcus aureus*. However, the combination of blue light and photosensitizers significantly inhibited bacterial viability. Riboflavin achieved 49.0±4.8% inhibition within 10 minutes, indicating a rapid but transient effect, whereas curcumin elicited a slower yet sustained antibacterial response, achieving 34.2 ± 1.6% inhibition after 30 minutes. Computational toxicity predictions suggested no clear evidence of skin irritation; however, a potential for skin sensitization remains. These findings support the potential of riboflavin- and curcumin-based PDI using Omega Light LED as a promising non-antibiotic approach for managing *Staphylococcus aureus* infections in AD and AK.

Keywords: *curcumin; photodynamic inactivation; riboflavin; skin disease; Staphylococcus aureus*

1. Introduction

The prevalence of Atopic Dermatitis (AD) and other skin-related conditions has been increased significantly in developing countries, including Indonesia. Recent studies indicate that approximately 22.6% of children in Asia are affected by AD, while the prevalence among adults is approximately 1.2% (Bylund et al., 2020). Similarly, the incidence of Actinic Keratosis (AK), a precancerous skin lesion, has also increased, with recent data estimating a prevalence of 14% (George et al., 2024).

AD and AK are frequently complicated by secondary microbial infections, particularly those caused by *Staphylococcus aureus* (Krueger et al., 2022). In addition, other microorganisms such as *Candida albicans* (Javad et al., 2015; Kobiela et al., 2022),

Malassezia furfur (Glatz et al., 2015; Navarro-Triviño & Ayén-Rodríguez, 2022), and herpes simplex virus (Traidl et al., 2021), are often found colonizing the skin of AD patients. In AK, colonization by β-human papillomavirus has been reported, suggesting that microbial factors may influence disease progression and immune responses (Galati et al., 2020). These polymicrobial communities often form biofilms, which contribute to persistent inflammation and increase resistance to conventional antimicrobial therapies.

The growing challenge of antimicrobial resistance necessitates the development of alternative therapeutic strategies. One such strategy is Photodynamic Inactivation (PDI), a technique that combines a photosensitizing agent, visible light, and molecular oxygen to generate reactive oxygen species (ROS). These ROS, particularly singlet oxygen, inflict oxidative damage on microbial cells, leading to their inactivation (Juan et al., 2021). Beyond its cytotoxic effects, PDI demonstrates a significant ability to disrupt microbial biofilms, which exhibit high resistance to conventional antimicrobial therapies (Warrier et al., 2021). PDI can interfere with microbial quorum-sensing systems, thereby hindering intercellular communication essential for coordinating pathogenic behaviors (Fekrirad et al., 2019). Additionally, this approach has been reported to suppress the expression of virulence determinants, thereby reducing the pathogenic potential of microorganisms (Hetta et al., 2024).

To date, most research on PDI has focused on food safety applications. Natural pigments such as curcumin and riboflavin have been successfully utilized as photosensitizers (PS) to inactivate pathogens on fresh produce and food-contact surfaces, offering advantages in terms of safety, biodegradability, and their dual functionality as colorants (Suksaeree & Monton., 2024). At the practical level, curcumin has demonstrated the ability to eliminate pathogenic microorganisms in fresh produce, including apples (Song et al., 2020; Nguyen et al., 2023), pineapples (Zou et al., 2021), and assorted vegetables (de Oliveira et al., 2018). Likewise, riboflavin has been proven effective in inactivating the Tulane virus on blueberries (Kingsley et al., 2018).

Despite these promising outcomes in food-related applications, the clinical potential of natural photosensitizers for managing cutaneous infections remains underexplored, particularly in cases of AD and AK. The superficial nature of these skin conditions makes them ideal candidates for PDI, as they are easily accessible to light. A key novelty of this study lies in the direct comparison between riboflavin and curcumin as natural photosensitizers for PDI, providing new insights into their relative antimicrobial efficacy against *Staphylococcus aureus* under identical experimental conditions. Furthermore, recent developments in light-based technologies have made light sources more accessible and easier to implement in clinical settings. In this study, the Omega Light LED system represents a feasible approach for dermatological applications, delivering low-level light therapy (LLLT) across multiple wavelengths compatible with various natural photosensitizers. Furthermore, an in silico toxicity assessment was performed to support its potential application in managing cutaneous infections.

2. Objectives

In this study, we investigated the potential of riboflavin and curcumin as natural photosensitizers in PDI, using the Omega Light LED as the irradiation source. The primary objective was to evaluate their antimicrobial efficacy against *Staphylococcus aureus*, a major contributor to infections in AD and AK.

3. Materials and Methods

Staphylococcus aureus (ATCC 25923) was employed as the test organism. Riboflavin and curcumin obtained from Sigma-Aldrich were utilized as natural photosensitizers. PDI was carried out using two first-generation Omega LED Light devices (O'melon, South Korea), which emit light at three distinct wavelengths: red (λ = 640 nm), blue (λ = 423 nm), and green (λ = 532 nm) (Figure 1). The intensity of each light source was measured using a digital lux meter (Krisbow KW06-291). In silico skin toxicity prediction of the photosensitizers was assessed using three publicly available computational tools, including Toxtree version 3.1.0. (Patlewicz et al., 2008), Pred-Skin 3 (Alves et al., 2016, 2018; Borba et al., 2020; Braga et al., 2017), and pkCSM (Pires et al., 2015).

Figure 1 Omega light-emitting diode (LED) phototherapy device (O'melon). Adapted from the Tokopedia e-commerce website

3.1 Preparation Stage

Photosensitizer solutions were prepared in a laminar airflow (LAF) cabinet under aseptic conditions. Stock solutions of the natural pigments riboflavin and curcumin (1.5% w/v) were prepared individually by dissolving each compound in dimethyl sulfoxide (DMSO). These stock solutions were subsequently diluted with distilled water to achieve a concentration of 0.15%, ensuring that the DMSO content remained below 1% (v/v) in each solution. The dissolution process was facilitated using an ultrasonicator and a vortex mixer. The solutions were stored under light-protected conditions at 4 °C to prevent photodegradation.

Bacterial suspensions of *Staphylococcus aureus* were prepared using Mueller-Hinton Agar (MHA) and Mueller-Hinton Broth (MHB). MHA slants were prepared and stored at 4 °C. For cultivation, the bacterial strain was inoculated onto a solidified MHA surface and incubated at 37 °C for 18 hours to allow optimal growth. A single colony was then transferred into 9 mL of MHB and incubated for 18 hours at 37 °C to obtain an actively growing bacterial suspension. The bacterial concentration was standardized to approximately 1.5×10^8 CFU/mL (8.18 log CFU/mL), corresponding to an optical density (OD_{600}) range of 0.08–0.10, as measured using a UV-Visible spectrophotometer (Shimadzu UV-1240).

3.2 Effect of Light Type on PDI Activity

The effect of light wavelength on PDI activity was evaluated by exposing *Staphylococcus aureus* suspensions to different light treatments in a 96-well microplate. A volume of 180 µL of bacterial suspension 8.18 log CFU/mL was added to each well, followed by 20 µL of photosensitizer solution (0.15% w/v). The mixture was homogenized to yield a final volume of 200 µL per well, resulting in a final photosensitizer concentration of 0.015% (w/v). Experimental concentrations were selected based on prior studies and were subsequently optimized during preliminary trials (Djalil et al., 2023; Ferreira dos Santos et al., 2019). Experimental controls included: cell control (bacterial suspension with culture medium only, no dye, and no light), dye control (dye solution with medium, no bacterial cells), solvent control (medium containing DMSO at the same final concentration used in treatments), and medium control (culture medium alone). All plates were incubated in the dark for 30 minutes at 37 °C to ensure sufficient interaction between the photosensitizer and bacterial cells. After incubation, the absorbance of each well was measured at 595 nm using a microplate spectrophotometer (ELISA reader). The influence of light wavelength on antimicrobial efficacy was evaluated by maintaining a constant dye concentration (0.015%) and illumination duration (30 minutes), while varying the type of LED light. The samples were irradiated using an Omega LED Light at three different wavelengths: red (λ = 640 nm), blue (λ = 423 nm), and green (λ = 532 nm). All experiments were conducted at ambient temperature. The intensity of each LED source was measured using a digital lux meter to ensure consistent light exposure across treatments. Bacterial viability was assessed by measuring the absorbance at 595 nm using an ELISA reader. The reduction in optical density (OD) was then compared to that of the corresponding control cells, with corrections applied for background absorbance from the medium and the photosensitizer.

3.3 Dark Toxicity Assay

Dark toxicity assays were conducted to evaluate the cytotoxic effects of the photosensitizers without light activation. *Staphylococcus aureus* suspensions (8.18 log CFU/mL) were aliquoted into 96-well microplates, with 180µL of bacterial suspension and 20µL of natural pigment solution (0.15% w/v) added to each well, resulting in a final dye concentration of 0.015% (w/v) and a total volume of 200 µL per well. To ensure optimal interaction without unintended light activation, the plates were first incubated in complete darkness at 37 °C for 30 minutes, followed by an additional 30-minute incubation at ambient temperature. Bacterial viability was assessed by measuring the absorbance at 595 nm using an ELISA reader. Results were compared with those of untreated control wells to determine whether the photosensitizers exhibited any dark toxicity effect.

3.4 Effect of Light Exposure Time on PDI Activity

The effect of illumination time on PDI efficacy was evaluated by mixing 180 µL of *Staphylococcus aureus* suspension with 20 µL of 0.15% photosensitizer solution in each well of a 96-well plate, resulting in a final dye concentration of 0.015%. Control groups included cell, dye, solvent, and medium controls. The plate was exposed to the optimal LED light wavelength for 10, 30, and 60 minutes at room temperature. Bacterial viability was assessed by measuring the absorbance at 595 nm using an ELISA reader.

3.5 Skin Toxicity Prediction

The chemical structures and Simplified Molecular-Input Line-Entry System (SMILES) notations of the natural pigment photosensitizers were sourced from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and used for skin toxicity prediction. Computational analysis was conducted using three freely available in silico tools: Toxtree, Pred-Skin, and pkCSM. The two-dimensional structures and corresponding SMILES of each compound are shown in Figure 2.

3.6. Statistical Analysis

Quantitative measurements were conducted in triplicate, and the results are expressed as mean ± standard deviation (SD). Paired *t*-tests were used to assess differences within the same group (at 0 and 30 minutes). All statistical analyses were performed using IBM SPSS Statistics for Windows version 25 (IBM, 2017), with statistical significance set at $p < 0.05$.

4. Results

Riboflavin and curcumin demonstrated significant inhibitory effects on the growth of *Staphylococcus aureus* when exposed to appropriate light wavelengths (Figure 3). Significant bacterial reduction was observed in the riboflavin–blue light and curcumin–blue light groups ($p < 0.05$), suggesting effective photoactivation of both compounds. The involvement of PDI as the underlying mechanism was confirmed by the requirement of three essential components: photosensitizer, light exposure, and molecular oxygen. Control experiments without light showed no significant bacterial inhibition, indicating that neither riboflavin nor curcumin alone was effective in the absence of photoactivation (Figure 4). Additionally, no statistically significant changes in bacterial viability were observed between 0 and 30 minutes in samples treated with riboflavin or curcumin alone without light ($p > 0.05$), reinforcing the necessity of all three components for effective PDI.

The Omega LED light devices were used as the light sources in this study. The measured intensities for blue (423 nm), green (532 nm), and red (640 nm) light were 2270, 1388, and 759 lux, respectively, with blue light exhibiting the highest output.

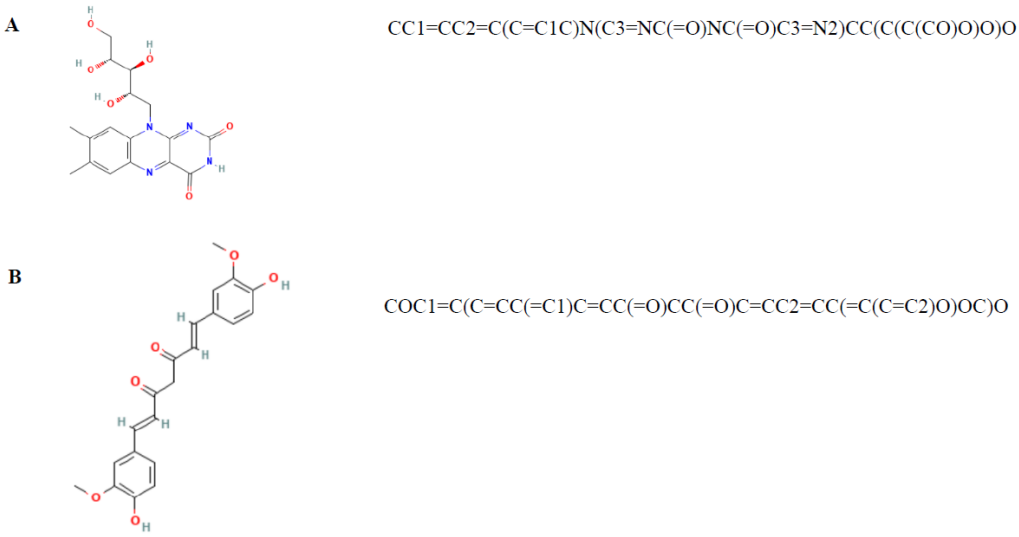

Figure 2 Chemical structures and SMILES representations of (A) riboflavin, (B) curcumin. Adapted from PubChem

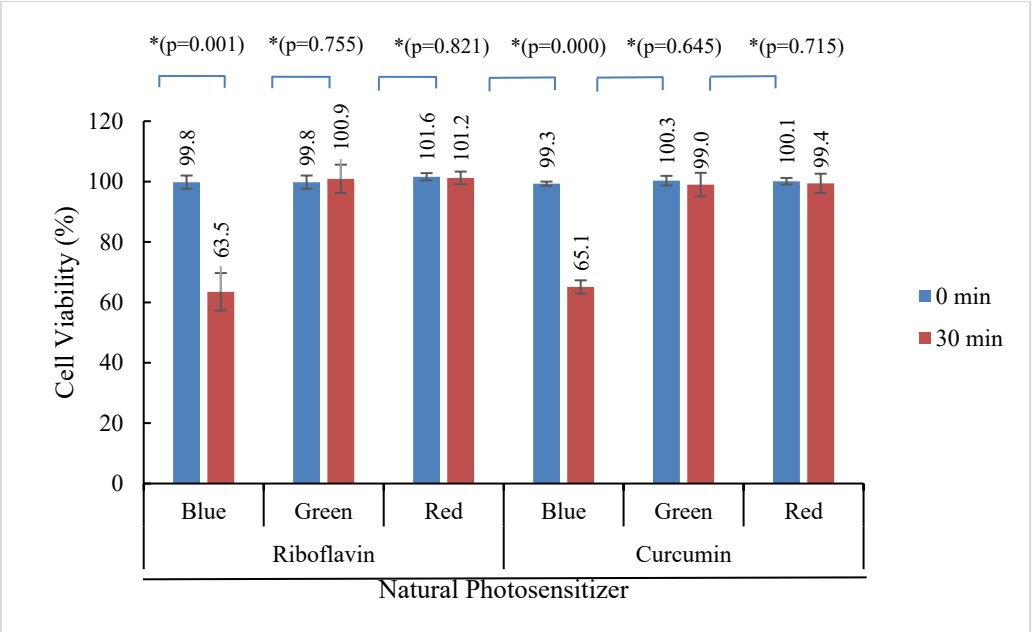

Figure 3 Percentage viability of *Staphylococcus aureus* after photodynamic treatment under different light wavelengths and intensities: red (640 nm, 2,270 lux), blue (423 nm, 1,388 lux), and green (532 nm, 759 lux). The photosensitizer concentration and irradiation time were fixed at 0.015% and 30 minutes, respectively. Significant reductions in bacterial viability were observed in the riboflavin-blue and curcumin-blue ($p < 0.05$) groups. The data represent the mean values from three independent experiments performed under identical conditions

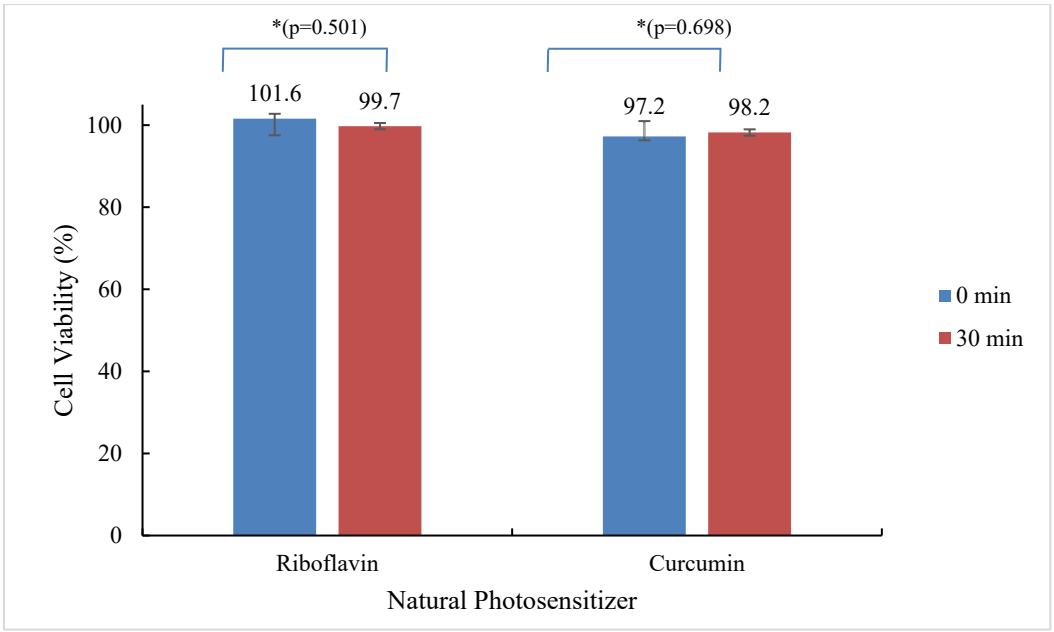

Figure 4 Percentage viability of *Staphylococcus aureus* without light exposure. The photosensitizer concentration and incubation time were fixed at 0.015% and 30 minutes, respectively. No statistically significant differences were observed when comparing bacterial viability at 0 minutes and 30 minutes in either the riboflavin or curcumin groups ($p > 0.05$). The data represent the mean values from three independent experiments performed under identical conditions

The efficacy of PDI was influenced by the type of light used. Both riboflavin and curcumin exhibited significantly enhanced antimicrobial activity under blue light exposure (Figure 3). In addition to light type and intensity, the duration of exposure also played a critical role in the effectiveness of the photosensitizers against *Staphylococcus aureus*. As shown in Figure 5, riboflavin achieved its maximal inhibitory effect within 10 minutes of irradiation (49.0 ± 4.8%). In contrast, curcumin exhibited a gradual, time-dependent increase in antimicrobial activity, with inhibition reaching 49.6 ± 1.0% after 60 minutes of light exposure.

In addition to the dark toxicity assay, the safety profile of the photosensitizers was evaluated using computational prediction tools, including Toxtree, Pred-Skin 3.0, and pkCSM (Table 1). According to Toxtree predictions, the compounds are not expected to cause skin irritation or corrosion; however, potential for skin sensitization was identified. In contrast, pkCSM predicted no potential for skin sensitization. Further assessment of using Pred-Skin 3.0 supported the possibility of sensitization. Bayesian analysis from Pred-Skin 3.0 suggested that both compounds are probable skin sensitizers, with a high confidence level in the prediction.

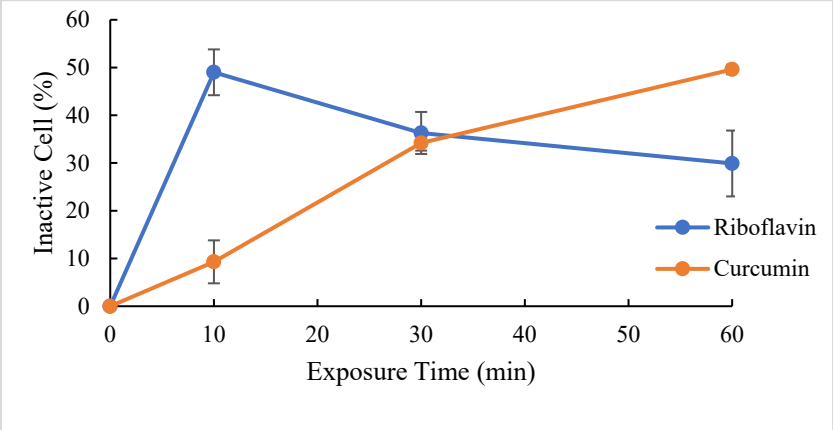

Figure 5 Percentage viability of *Staphylococcus aureus* after photodynamic treatment under blue light (λ = 423 nm, 2,270 lux) at different exposure durations: 10, 30, and 60 minutes. The concentration of photosensitizers was fixed at 0.015%. Data represents the mean ± SD from three independent experiments conducted under identical conditions

Table 1 *In silico* skin irritation and sensitization predictions of riboflavin and curcumin obtained using Toxtree 3.1.0, Pred-Skin 3.0, and pkCSM computational tools

Skin Toxicity Prediction	Compounds	
	Riboflavin	**Curcumin**
Toxtree 3.1.0		
Skin irritation	Not irritation or corrosive to skin	Not irritation or corrosive to skin
Skin sensitivity	Alerts for acyl transfer agent identified	Alert for Michael acceptor identified Alert for Schift base formation identified
Pred-Skin 3.0		
Prediction DPRA[1]	Sensitizer (confiability 82.2%)	Sensitizer (confiability 93.4%)
Prediction KeratinoSens[2]	Non-sensitizer (confiability 87.9%)	Sensitizer (confiability 95.5%)
Prediction h-CLAT[3]	Non-sensitizer (confiability 68.1%)	Non-Sensitizer (confiability 55.0%)
Prediction LLNA[4]	Non-sensitizer (confiability 100%)	Sensitizer (confiability 99.9%)
Prediction HRIPT/HMT[5]	Sensitizer (confiability 96.6%)	Sensitizer (confiability 99.0%)
Bayesian outcome[6]	Sensitizer (confiability high)	Sensitizer (confiability high)
pkCSM		
Skin sensitisation	No	No

Model predictions: [1]DPRA = Direct Peptide Reactivity Assay; [2]KeratinoSens = Sensitization of human keratinocytes; [3]h-CLAT = Human Cell Line Activation Test; [4]LLNA = Murine local lymph node assay; [5]HRIPT/HMT = Human repeated insult patch test and human maximization test; [6]Bayesian consensus = Integrated prediction derived from averaging the outputs of multiple models

5. Discussion

Our study demonstrated that riboflavin and curcumin, applied at a concentration of 0.015% (1.5 mg/mL) and activated by blue light (423 nm, 2,270 lux, 30 minutes), effectively reduced the growth of *Staphylococcus aureus*. Specifically, riboflavin led to a 36.3% reduction in bacterial viability (7.69 log CFU/mL), while curcumin achieved a 34.2% reduction (7.66 log CFU/mL). Although the reductions were moderate compared to high-intensity protocols, the relatively low level of light exposure in our study indicates that PDI can provide a safer, energy-efficient approach for managing skin-related infections.

A light-only control was excluded because previous studies reported that blue light at 423 nm and 2,270 lux have no significant effect on *S. aureus* viability, including antibiotic-resistant strains (Dai et al., 2013; Makdoumi et al., 2019; Ngo et al., 2023). Therefore, the observed antimicrobial effects can be attributed primarily to photosensitizer-mediated PDI.

To facilitate comparison with existing literature, we estimated the illuminance of the light source by converting irradiance (mW/cm²) to lux, based on the luminous efficacy of blue light at the specified wavelength. A previous study conducted by Li et al. (2020) reported a significant bactericidal effect using a curcumin-loaded chitosan spray (25 μmol/L or 0.009 mg/mL) combined with high-intensity blue LED light (460-465 nm, ~115,000 lux) for 10 minutes, which reduced *Staphylococcus aureus* viability to 5.0 log CFU/mL. For riboflavin, prior work has typically employed UVA activation to induce bacterial inactivation. In contrast, our study employed blue light as the activation source but still produced comparable antibacterial effects. Adding to this line of evidence, Makdoumi et al. (2019) reported the complete elimination of methicillin-resistant *Staphylococcus aureus* (MRSA) using riboflavin (1.0 mg/mL) and blue light (450 nm, ~12,059 lux) for 30 minutes. Interestingly, the same study also reported that similar treatment conditions completely inactivated keratinocytes. This observation suggests that the application of light-activated riboflavin may extend beyond antimicrobial purposes. Since skin disorders such as psoriasis (Makuch et al., 2022; Kruanamkam et al., 2024), atopic dermatitis (Ogonowska et al., 2023), and actinic keratosis (Pihl et al., 2023) involve excessive growth of keratinocytes, this approach may offer a way to selectively reduce these overactive cells, thereby helping to manage such conditions more effectively.

PDI has shown promising therapeutic potential in treating AD, particularly when 5-aminolevulinic acid is used as a photosensitizer, as evidenced by studies conducted in patients with chronic hand eczema (CHE) (Kremer et al., 2020). However, studies investigating natural pigments as photosensitizers for treating AD and AK remain highly limited, highlighting the need for further investigation. This need becomes even more pressing considering the role of *Staphylococcus aureus*, a predominant microorganism in AD and AK, which exhibits high colonization rates on the skin of individuals affected by these conditions (Nada et al., 2012; Sreepian & Sreepian, 2025). The presence of this bacterium contributes to disease severity by producing toxins and superantigens that aggravate inflammation and delay the healing process (Kim et al., 2019; Wang et al., 2024). By inhibiting the growth of *Staphylococcus aureus*, PDI has the potential to reduce inflammation, decrease the bacterial load in AD and AK lesions (Koo & Kim, 2022; Ogonowskaet al., 2023). In addition to its antimicrobial effect, PDI may confer therapeutic benefits through two principal mechanisms: antimicrobial activity and immunomodulation. Although direct investigations on the application of PDI in AD remain limited, its fundamental mechanism, based on the generation of ROS, closely resembles that of conventional phototherapy.

PDI operates through the synergistic action of three essential components: a photosensitizer (PS), molecular oxygen, and light of a specific wavelength. The process begins when the PS, absorbed by cells, such as pathogens, is activated by exposure to light. Upon irradiation, the PS absorbs photons and transitions from its stable ground state (^{1}PS) to an unstable excited singlet state (^{1}PS*). The ^{1}PS* molecule may return to the ground state by releasing energy as fluorescence or heat or undergo intersystem crossing, resulting in a more stable excited triplet state (^{3}PS*). This triplet state plays a central role in two major photochemical pathways. In type II reactions, which predominate in PDI, ^{3}PS* transfers energy directly to molecular oxygen (O_2), producing singlet oxygen ($^1O_2$), a highly cytotoxic ROS. In type I reactions, ^{3}PS* interacts with cellular substrates (e.g., lipids or proteins), generating free radicals or radical ions. These can further react with oxygen to form additional ROS, such as hydroxyl radicals (•OH), superoxide anion (O_2^-•), and hydrogen peroxide (H_2O_2). The ROS causes irreversible oxidative damage to vital cellular components such as membranes, proteins, and nucleic acids. This damage ultimately leads to microbial or cellular death via necrosis or apoptosis, depending on exposure conditions (Correia et al., 2021; Almenara-Blasco et al., 2024; Mulyani et al., 2024).

This study did not include direct quantification of reactive oxygen species (ROS); however, the ability of both curcumin and riboflavin to generate singlet oxygen upon light activation is well established. Chignell et al. (1994) reported that curcumin, at a concentration of 50 μM and exposed to light above 400 nm, produced singlet oxygen with a quantum yield (ΦΔ) of approximately 0.11, as determined using phosphorescence spectroscopy. In comparison, riboflavin at 100 μM exhibited a higher quantum yield of 0.48, measured directly via 1270 nm luminescence detections (Chacon et al., 1988; Wolnicka-Glubisz et al., 2020). These findings support the involvement of singlet oxygen as a major cytotoxic species in photodynamic inactivation (PDI) mediated by natural photosensitizers. ROS generated during PDI have been shown to inhibit the proliferation of hyperactive immune cells, downregulate key pro-inflammatory cytokines such as IL-4, IL-13, and TNF-α, and suppress the activity of dendritic cells as well as Th2-polarized T helper cells. These immunomodulatory effects underscore the potential of PDI as a promising adjunctive therapy to address immune dysregulation in AD (Borgia et al., 2022).

Furthermore, our study demonstrated that riboflavin and curcumin, used as photosensitizers, can effectively inactivate *Staphylococcus aureus*, a bacterium commonly implicated in AD and AK pathogenesis. Nonetheless, several important limitations must be acknowledged. First, although in vitro results are encouraging, they do not fully replicate the complex physiological environment of human skin, including the presence of sebum, the barrier function of the stratum corneum, and the role of a balanced skin microbiome. Second, validation using three-dimensional human skin models, which more accurately simulate in vivo conditions, has not yet been performed. Third, the immune response and skin reactivity to ROS generated during PDI cannot be comprehensively assessed through cellular-level studies alone. Therefore, future research should employ more physiologically relevant models, such as reconstructed human skin, followed by in vivo validation in animal models and eventual clinical trials in patients with AD and AK.

Despite these limitations, the findings from our study provide additional insights into the practical application of PDI, particularly regarding the comparative effectiveness of different photosensitizers against *Staphylococcus aureus*. The results of this study indicate that riboflavin is more effective in rapidly inactivating *Staphylococcus aureus*, achieving optimal inhibition within just 10 minutes of light exposure. In contrast, curcumin showed a continuous inhibitory trend, with increasing inactivation observed up to 60 minutes of irradiation (Figure 5). The duration of irradiation is a critical factor influencing the success of PDI, including its impact on *Staphylococcus aureus*. In this context, the three key components of PDI, photosensitizers (riboflavin vs. curcumin), light (wavelength, intensity, and duration), and molecular oxygen saturation, collectively contribute to the overall antimicrobial efficacy.

Prolonged exposure to irradiation typically increases ROS generation, intensifying damage to microbial cells. Nonetheless, this effect does not always scale linearly. After surpassing a specific limit, the antimicrobial efficacy may reach a plateau, potentially due to depletion of the photosensitizer, limited oxygen availability, or adaptive resistance mechanisms within the bacteria. Riboflavin, while highly water-soluble, is also photolabile and susceptible to photochemical degradation (Sheraz et al., 2014). Riboflavin undergoes significant degradation when exposed to ultraviolet and visible light, leading to the formation of by-products such as lumichrome and lumiflavin, which possess reduced photosensitizing capability (Huang et al., 2006). Under specific conditions, riboflavin degrades with a half-life of less than 8 minutes, likely explaining the decline in antimicrobial efficacy after 10 minutes of illumination (Remucal & McNeill, 2011). Nevertheless, under unmodified, native conditions, riboflavin demonstrates a faster inactivation profile than curcumin against *Staphylococcus aureus*.

Curcumin, on the other hand, suffers from poor aqueous solubility, which affects its bioavailability (Górnicka et al., 2023). More time is required to penetrate microbial cells and generate sufficient ROS. Although curcumin exhibits a slower onset of action than other photosensitizers due to its poor aqueous solubility, it has shown the capacity to sustain or improve its efficacy under extended light exposure, mainly because of its photostability. Notably, curcumin continues to exhibit a measurable inhibitory effect against *Staphylococcus aureus* even after 60 minutes of irradiation. Curcumin's efficacy as a photosensitizer, especially for skin-related treatments, can be substantially improved through suitable formulation approaches. Microemulsions (Liu et al., 2016), gels (Crusca et al., 2025), and nanoparticles (Gomez et al., 2019) are known to enhance the solubility and stability of this compound.

The effectiveness of PDI is also strongly influenced by the characteristics of the light source, light dose, and duration of light exposure (Kim & Darafsheh, 2020). In this study, the Omega Light LED

was employed. Widely used in dermatology and aesthetic medicine, this device has effectively treated various skin concerns, including acne, inflammation, pigmentation disorders, and premature aging (Glass, 2021). Its use, therefore, can be extended beyond cosmetic applications to therapeutic interventions for skin-related infections. In the context of this study, the blue light spectrum emitted by the Omega Light LED is well-suited to excite the photosensitizers used (riboflavin and curcumin). The combination of cost-effectiveness and accessibility of both the photosensitizers and the LED source highlight the potential of this technique for expanded use in clinical or practical applications. Omega Light LED technology operates based on low-level light therapy (LLLT) principles, which utilize specific wavelengths of LEDs to stimulate biological responses at the cellular level without causing thermal tissue damage (Lin, 2018). The device is manufactured by O'melon, a well-established South Korean company with over two decades of expertise in developing light-based medical and aesthetic technologies (Ablon, 2018). Moreover, the device is commercially available through various e-commerce platforms in Indonesia, further supporting its practicality for localized applications and underscoring its economic viability.

Furthermore, an in silico toxicity assessment was carried out as a complementary approach to the experimental findings, aiming to characterize the safety profile of the photosensitizing agents. This evaluation utilized several computational tools, including Toxtree 3.1.0, Pred-Skin 3.0, and pkCSM (Table 1). Since PDI involves the activation of photosensitizers by light, it is essential to ensure that these compounds do not induce adverse dermatological effects upon exposure. While in silico toxicity assessments provide valuable preliminary insights, they must be validated through laboratory-based toxicological experiments to ensure the safety of the agents.

The Toxtree software identifies potential toxicity risks by detecting structural alerts related to skin toxicity using a rule-based decision-tree approach. According to the predictions, neither riboflavin nor curcumin is expected to cause skin irritation or corrosion. Nevertheless, the possibility of skin sensitization could not be ruled out definitively. Riboflavin may pose a sensitization risk due to its potential as an acylating agent. In the case of curcumin, the presence of an α,β-unsaturated carbonyl group enables it to react with nucleophiles through Michael addition, and its capacity to undergo Schiff base formation further suggests a potential for skin sensitization (Chaudhari et al., 2015). Nonetheless, Toxtree has limitations, especially in predicting the toxicity of compounds with intricate molecular architectures. Its accuracy can be affected by false-positive or false-negative outcomes because the model does not consider important pharmacokinetic parameters such as bioavailability, metabolic processes, and chemical stability. Toxtree has demonstrated an accuracy of around 65% in prior evaluations (Golden et al., 2023).

Toxicity predictions for skin sensitization were also performed using the Pred-Skin 3.0 tool. Interpreting the results from the Pred-Skin software requires an understanding of the output and the underlying algorithm. The model generates a probability score between 0 and 1, where values approaching 0.5 indicate uncertainty in the prediction. The applicability domain indicates whether the tested compound falls within the data range of the model (Borba et al., 2020). According to in vitro testing methods, riboflavin is generally classified as a non-sensitizer with a confidence score greater than 50%. These results are consistent with studies conducted on rabbits (EFSA Panel on Additives and Products or Substances used in Animal Feed (EFSA FEEDAP Panel) et al., 2018). However, data from DPRA and human testing (HRIPT/HMT) indicate riboflavin as a sensitizer, with a high confidence level of 96.6%. Human data are considered the most clinically relevant, and thus the Bayesian outcome, based on an integrative analysis, concludes that riboflavin is a sensitizer. For curcumin, the tool predicts it to be a sensitizer, supported by both in vitro test methods (except for h-CLAT, which showed low reliability) and human testing, both of which demonstrated high reliability (> 93%). Therefore, to avoid skin sensitization, protective measures against natural light exposure should be considered for individuals using curcumin (Chaudhari et al., 2015). The non-sensitizer predictions produced by the pkCSM model for both compounds may be attributed to their chemical structures and molecular features, which do not exhibit significant similarity to those of established skin-sensitizing agents represented in the model's training dataset. This structural dissimilarity could have led the algorithm to classify them as lacking sensitization potential.

This study has several limitations. Notably, a treatment group exposed to light alone (without the photosensitizer) was not included, nor was a positive control group treated with conventional antibiotics. Despite these limitations, the combination of Omega

Light LED and a natural pigment photosensitizer in photodynamic inactivation (PDI) was successfully demonstrated. Future studies are required to optimize the delivery of photosensitizers, particularly by addressing the limitations of physicochemical properties and light penetration. Formulations such as nanoparticle-based hydrogels are considered promising for enhancing the efficacy of photosensitizers, which should be further validated through in vivo studies involving patients with atopic dermatitis (AD) or actinic keratosis (AK).

6. Conclusion

This study shows that both riboflavin and curcumin can serve as effective photosensitizers in the photodynamic inactivation of Staphylococcus aureus. Their antibacterial potential suggests possible therapeutic applications for skin conditions such as atopic dermatitis and actinic keratosis. Riboflavin exhibits a rapid antibacterial effect (49.0% at 10 minutes), while curcumin displays slower but sustained activity, achieving over 50% inactivation at 60 minutes under the experimental conditions employed. These findings suggest that curcumin offers greater photochemical stability over time. The application of blue light, particularly using the Omega Light LED system, was found to enhance the photodynamic effectiveness of both compounds. Although these agents show promising therapeutic potential, computational toxicity predictions suggest a potential risk of skin sensitization. These results underscore the need for carefully formulated approaches and protective strategies to optimize their safety and efficacy for clinical applications.

7. Abbreviations

AD	Atopic Dermatitis
AK	Actinic Keratosis
PDI	Photodynamic Inactivation
LED	Light-Emitting Diode
ELISA	Enzyme-Linked Immunosorbent Assay
PS	Photosensitizers
ROS	Reactive Oxygen Species
LLLT	Low-Level Light Therapy
LAF	Laminar Airflow
DMSO	Dimethyl Sulfoxide
MHA	Mueller-Hinton Agar
MHB	Mueller-Hinton Broth
CFU	Colony-Forming Units
OD	Optical Density
SMILES	Simplified Molecular-Input Line-Entry System
SD	Standard Deviation
MRSA	Methicillin-Resistant Staphylococcus aureus
CHE	Chronic Hand Eczema
O_2	Molecular Oxygen
$^1O_2$	Singlet Oxygen
^1PS	Ground State of Photosensitizer
$^1PS^*$	Excited Singlet State of Photosensitizer
$^3PS^*$	Excited Triplet State of Photosensitizer
•OH	Hydroxyl Radicals
$O_2^{-}\bullet$	Superoxide Anion
H_2O_2	Hydrogen Peroxide
DPRA	Direct Peptide Reactivity Assay
KeratinoSens	Sensitization of human keratinocytes
h-CLAT	Human Cell Line Activation Test
LLNA	Murine Local Lymph Node Assay
HRIPT/HMT	Human Repeated Insult Patch Test and Human Maximization Test
EFSA FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
UVA	Ultraviolet A

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9. CRediT Statement

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