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Styrax benzoin Emulgel for Burn Wound Healing: Formulation, Evaluation, and *in vivo* Study

(Emulgel *Styrax benzoin* untuk Penyembuhan Luka Terbakar: Formulasi, Penilaian dan Kajian *in vivo*)

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ABSTRACT

Burn-wound mortality is high, affecting 180,000 annually based on WHO's data in 2018, especially in low-to-middle-income countries. Antibiotic misuse leads to resistance, prompting the need for alternative treatments. Studies have shown the effectiveness of *Styrax benzoin* in wound treatment, highlighting the need to investigate the formulation and *in vivo* study for burn wound healing. This study aimed to determine the optimal *Styrax benzoin* emulgel formula and evaluate its effectiveness on burn wounds in mice. *Styrax benzoin* extract was analyzed using various chemical tests and LC-MS/MS. The optimal emulgel formula was determined using the simplex lattice design (SLD) method with variations in Hydroxypropyl Methylcellulose (HPMC) and carbopol 940 concentrations. An *in vivo* study measured burn wound reduction and was analyzed using one-way ANOVA and Tukey post hoc test. Chemical tests found the presence of alkaloids, tannins, triterpenoids, and flavonoids. LCMSMS analysis showed cinnamic acids and vanillin. The optimal emulgel formula, with a 2:1 ratio of HPMC to carbopol 940, demonstrated 4.954 s adhesion, 5.594 cm spreadability, and 314533.329 cPs viscosity. At a 10% concentration of *Styrax benzoin* ethanol extract, this emulgel achieved the highest burn wound healing rate of 75.83%, significantly reducing the wound area.

Keywords: Burn wound healing; carbopol 940; emulgel; hydroxypropyl methylcellulose; *in vivo*; *Styrax benzoin*

ABSTRAK

Kadar kematian akibat luka terbakar adalah tinggi dengan 180,000 kes setiap tahun berdasarkan data WHO pada tahun 2018, terutamanya di negara berpendapatan rendah dan sederhana. Penyalahgunaan antibiotik menyebabkan kerintangan yang mendesak pencarian rawatan alternatif. Penyelidikan ini telah menunjukkan keberkesanan *Styrax benzoin* dalam rawatan luka, menekankan keperluan untuk mengkaji formulasi dan kajian *in vivo* bagi penyembuhan luka terbakar. Kajian ini bertujuan untuk menentukan formula emulgel *Styrax benzoin* yang optimum dan menilai keberkesanannya terhadap luka terbakar pada tikus. Ekstrak *Styrax benzoin* dianalisis menggunakan pelbagai ujian kimia dan LC-MS/MS. Formula emulgel optimum ditentukan menggunakan kaedah reka bentuk kisi simpleks (SLD) dengan variasi dalam kepekatan Hidroksipropil Metilselulosa (HPMC) dan carbopol 940. Kajian *in vivo* mengukur pengurangan luka terbakar, dianalisis menggunakan ANOVA satu hala dan ujian pasca hoc Tukey. Ujian kimia mendapati kehadiran alkaloid, tanin, triterpenoid dan flavonoid. Analisis LCMSMS menunjukkan asid sinamat dan vanillin. Formula emulgel optimum dengan nisbah 2:1 HPMC kepada carbopol 940, menunjukkan masa lekat 4.954 saat, kebolehan penyebaran 5.594 cm dan kelikatan 314533.329 cPs. Pada kepekatan 10% ekstrak etanol *Styrax benzoin*, emulgel ini mencapai kadar penyembuhan luka bakar tertinggi sebanyak 75.83%, mengurangkan kawasan luka dengan ketara.

Kata kunci: Carbopol 940; emulgel; hidroksipropil metilselulosa; *in vivo*; penyembuhan luka bakar; *Styrax benzoin*

INTRODUCTION

The mortality rate caused by burn wounds is significantly high, with an estimated 180,000 deaths occurring annually based on WHO's data in 2018, particularly in low to middle-income regions such as Africa and Asia (Smolle et al. 2017). Infections from severe burn wounds can lead to death if not treated promptly and appropriately, often due to complications like sepsis and multi-organ failure (Kemkes 2019). While antibiotics such as amoxicillin, ampicillin, and synthetic drugs are commonly used for treatment, their persistent use can result in side effects and the development of antibiotic resistance (I. Wayan et al. 2019).

As an alternative, natural wound healing and anti-inflammatory agents, such as *Styrax benzoin*, offer promising treatment options (Abd El-Razek et al. 2022; Fadhilah & Imaniar 2019; Sohail Akhtar & Alam 2021). *Styrax benzoin*, commonly known as the frankincense tree, belongs to the *Styracaceae* family and is widely found in

subtropical or tropical areas, including North Sumatra, Indonesia. The resin, obtained from tapping the bark of 15-20-year-old trees, is highly valued for its medicinal properties (Minta Ito Melinda 2019). Benzoin resin contains various phytochemical compounds, including cinnamic acid, flavonoids, benzaldehyde, styrene, and triterpenoid derivatives like sumaresinolic acid and siaresinolic acid. Specifically, cinnamic acid has biological activity as an antibacterial, anti-inflammatory, and also wound-healing properties (Asih, Eti & Irmanida 2019). These properties are crucial in treating burn wounds, as the anti-inflammatory effect helps in reducing swelling, preventing infections, and promoting faster healing (Sohail Akhtar & Alam 2021; Subehan et al. 2020).

Given these benefits, this study aimed to develop an optimal emulgel formulation of *Styrax benzoin* and assess its effectiveness in burn wound healing in mice. An emulgel was chosen for this study because it combines the beneficial properties of both gels and emulsions, improving the penetration of active ingredients into the skin (Sani Ega et al. 2013). Additionally, emulgels offer ease of application, aesthetic appeal, and a soothing effect, making them particularly suitable for treating burn wounds (Nurasyfa et al. 2019).

MATERIALS AND METHODS

MATERIALS

The materials used included ethanol 96% (Merck), Whatman filter paper *Styrax benzoin* resin, hydroxypropyl methylcellulose (HPMC), carbopol 940, tween 80 (Merck), span 20 (Merck), olive oil, glycerin ((Wilmar Nabati Indonesia), sorbitol, sodium benzoate, triethanolamine (Petronas Chemicals), Bioplacenton® (Kalbe Farma), propylene glycol, Methylene blue (Merck KGaA), Bio Rat test animal feed, Xyla® (Interchemie), and Ketamine (Dexa Medica).

EXTRACTION AND PHYTOCHEMICAL ANALYSIS

Styrax benzoin resin (1000 g) was finely ground into powder, which was macerated in 1000 mL of 96% ethanol for 3 days. After filtration, the extract was concentrated using a rotary evaporator at 70 rpm, 60 °C, to obtain a viscous extract (Nora, Jamalum & Dedi 2021). Standard phytochemical tests were performed to detect the presence of major compounds such as flavonoids, tannins, alkaloids, saponins, and triterpenoids (Lisi, Runtuwene & Wewengkang 2017). The flavonoid test was conducted by adding a few drops of 5% ferric chloride ($FeCl_3$) solution into a test tube containing the ethanol extract of *Styrax benzoin*. A color change from orange-reddish to reddish-brown indicated the presence of flavonoids. Tannins were detected by adding 1% ferric chloride ($FeCl_3$) solution, which produced a blue-black or greenish-black coloration. Alkaloids were identified using Dragendorff's reagent after acidification with 2 N sulfuric acid (H_2SO_4); a reddish-brown precipitate indicated a positive result. Saponins were screened by heating the extract with water and adding 2 N HCl; the formation of stable froth or persistent foam indicated a positive test for saponins. The terpenoid test was performed by adding acetic acid and concentrated sulfuric acid (H_2SO_4) to the ethanol extract; a visible color change from orange-reddish to dark brown or blackish-brown confirmed the presence of terpenoids.

LC-MS/MS ANALYSIS

The LC-MS/MS analysis was conducted using the Acquity UPLC I-Class System coupled with a Xevo G2-S QTof mass spectrometer, integrated into the UNIFI Scientific Information System. This setup was chosen for its sensitivity and accuracy in detecting and quantifying phytochemicals in complex mixtures. The analysis was performed in full scan mode with a mass-to-charge ratio (m/z) range of 50 to 1200. Chromatographic separation was achieved using an Acquity UPLC HSS T3 C18 column (2.1 × 100 mm, 1.8 µm) at a column temperature of 40 °C. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B), with a gradient program optimized for separating the target compounds: 0 min 99:1 (A:B, v/v), 0.5 min 99:1 (A:B, v/v), 16 min 65:35 (A:B, v/v), 18 min 0:100 (A:B, v/v), and 20 min 99:1 (A:B, v/v). The flow rate was maintained at 0.6 mL/min, and a 10 µL injection volume was used. Key instrument parameters included a capillary voltage of 3.0 kV (ESI+) or 2.5 kV (ESI-), a cone voltage of 100 V, a cone gas flow of 1000 L/h, and a desolvation temperature of 500 °C. These conditions were selected to maximize the ionization and detection of *Styrax benzoin* components, ensuring comprehensive analysis.

EMULGEL FORMULATION

The emulgel formulation process was initiated by dissolving *Styrax benzoin* resin in 5% propylene glycol. The aqueous phase was prepared by dissolving Tween 80 in water, followed by heating, and the addition of the resin solution. Simultaneously, the oil phase was formed by mixing Span 20 with olive oil. These two phases were then homogenized to form an oil-in-water emulsion with a hydrophilic-lipophilic balance (HLB) value of 15.0 (Dita Nurlita, Yuli Ainun & Fadhilah 2020).

The emulgel was optimized using a combination of two gelling agents, HPMC and carbopol 940, at concentrations ranging from 0.5% to 2.5% individually. The gelling agents were prepared separately: carbopol 940 was dispersed in water and stirred while heating until a gel formed, with triethanolamine (TEA) added to adjust the pH to 4.5-6.5, while HPMC was dispersed in hot water and then combined with the carbopol 940 gel. The oil-in-water emulsion containing *Styrax benzoin* was then added to the gelling agent mixture, followed by other excipients and vigorous stirring to form the final emulgel. The optimization of the emulgel formula was guided by the

simplex lattice design (SLD) method, using Design Expert software (Version 13.0.0, Stat-Ease). The independent variables were the concentrations of two gelling agents: carbopol 940 and hydroxypropyl methylcellulose (HPMC), tested at five different ratio combinations to form five experimental formulations (F1–F5). The concentration levels of carbopol 940 and HPMC used were 0.5%, 1%, 1.5%, 2%, and 2.5% (all w/v), respectively (Christine & Nyi 2016; Dita Nurlita, Yuli Ainun & Fadhilah 2020). The detailed compositions of each formulation are presented in Table 1. Each formulation was evaluated for key response parameters, including viscosity, spreadability, and adhesion. The data were analyzed using the SLD model to generate polynomial equations describing the relationship between gelling agent composition and each response. The optimal formula was selected based on the desirability values close to one in spreadability, adhesion, and viscosity parameters.

EVALUATION AND STABILITY OF EMULGEL

The emulgel was evaluated for organoleptic properties, pH, homogeneity, spreadability, adhesion, viscosity, and emulsion type.

Organoleptic

Organoleptic testing involved assessing the texture, color, and odor of the emulgel, with acceptable criteria defined as a uniform texture, no odor or phase separation, and consistent color (Rahmi et al. 2019).

Homogeneity

Homogeneity was confirmed by applying 0.5 g of emulgel to a glass slide and ensuring a uniform texture without clumping under both macroscopic and microscopic examination (Uswatun et al. 2023).

pH

The pH was measured using a universal pH indicator to ensure it was within the 4.5-6.5 range suitable for skin application (Uswatun et al. 2023).

Spreadability

Spreadability was tested by placing 0.5 g of emulgel between two glass plates, applying a 50 g load for one minute, and then adding weights of 100 g, 150 g, and 250 g, each for one minute, with the spreadability diameter measured afterward. The optimal spreadability was defined as a diameter between 5 and 7 cm (Voigt 1994).

Adhesion

Adhesion was assessed by spreading 0.25 g of emulgel on a glass slide, covering it with another slide, and adding a 500 g load for one minute. The time taken for the slides to separate was recorded, with adhesion considered strong if the time exceeded one second (Dwi, Iwan & Hendri 2022; Voigt 1994).

Viscosity

Viscosity was measured using a HAAKE Viscotester D, with acceptable viscosity ranging from 2000 to 50000 cPs (Rahmi et al. 2019).

Stability

Stability testing was conducted at room temperature for three months and under freeze-thaw conditions for three cycles, each cycle consisting of 24 h at -20 °C with ±65% humidity, followed by 24 h at 40 °C with ±75% humidity, to ensure the emulgel maintained its properties under storage and extreme conditions (Endah, Faramita & Ishak 2021; Rina 2020).

TABLE 1. Composition of emulgel formulations

Component	F1	F2	F3	F4	F5
Styrax benzoin ethanolic extract	5	5	5	5	5
Carbopol 940	0.5	1.5	2.0	1.0	2.5
HPMC	2.5	1.5	1.0	2.0	0.5
Tween 80	2.65	2.65	2.65	2.65	2.65
Span 20	2.35	2.35	2.35	2.35	2.35
Glycerin	15	15	15	15	15
Sorbitol	10	10	10	10	10
Triethanolamine (TEA)	0.3	0.3	0.3	0.3	0.3
Olive oil	5	5	5	5	5
Sodium benzoate	0.5	0.5	0.5	0.5	0.5
Propylene glycol	5	5	5	5	5
Distilled water	ad 20 mL	ad 20 mL	ad 20 mL	ad 20 mL	ad 20 mL

in vivo STUDY

The *in vivo* study was performed using male mice (25-30 g, aged 8-12 weeks, strain *Deutschland Denken Yoken*. The mice were acclimatized for one week prior to the experiment. To induce burn wounds, the back hair of the mice was shaved, and they were anesthetized with a mixture of ketamine and xylazine (7:1) administered intraperitoneally at a dose of 0.1 mL/20 g body weight (IACUC 2023; Blaise et al. 2020). A 1.1 × 1.2 cm hot metal plate was applied to the back skin for 5 s to create the burn wounds (Nelky 2021). The mice were then divided into five groups (n=6 per group): a positive control group treated with Bioplacenton®, a negative control group treated with emulgel base, and three experimental groups treated with *Styrax benzoin* emulgel at concentrations of 1%, 5%, and 10%. The treatments were applied twice daily, and the wound healing process was monitored for 15 days using Macbiophotonic ImageJ software for wound area measurement. Photographs were taken daily to document the healing process. This study was approved by the Ethics Committee of the Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia (Approval number: 15/03/KEP-FKIKUAJ/2023). The percentage of burn wound healing was calculated using the formula (Arini, Nuriyatul & Noval Adi 2021):

$$\% \text{ Area of wound healing} = (\text{Initial wound area} - \text{Final wound area})/(\text{Initial wound area}) \times 100\%$$

DATA ANALYSIS

Data were analyzed using Design Expert 13.0.0 software with the SLD method to determine the optimal emulgel formula, characterized by desirability values close to one for spreadability, adhesion, and viscosity. Results were expressed as mean ± standard deviation, and burn wound healing data were analyzed using one-way ANOVA followed by Tukey post hoc test to assess the significance between treatment groups ($p<0.05$) (Arini, Nuriyatul & Noval Adi 2021).

RESULTS AND DISCUSSION

The percentage yield of *Styrax benzoin* ethanol extract obtained via maceration was 91.81%. The crude extract was dark brown with a distinctive odor. Phytochemical screening showed the presence of flavonoids, tannins, alkaloids, and terpenoids (Table 2). This finding contrasts with previous research by Nora, Jamalum and Dedi (2021), which detected saponins in *Styrax benzoin* ethanol extract. This discrepancy could be attributed to differences in extraction techniques, plant chemotype, sample origin, or the sensitivity and specificity of the qualitative tests used. Furthermore, hydrophobic interactions and the formation of precipitates may have interfered with the detection of saponins (Jayusman & Fiani 2019). Although saponins are known for their anti-inflammatory and wound-healing effects (Razika et al. 2017; Wijesekara, Luo & Xu 2024), several studies have highlighted that the main bioactive constituents responsible for burn wound healing in *Styrax benzoin* are its phenolic compounds like cinnamic acid and vanillin. These constituents exhibit significant antioxidant and anti-inflammatory properties, which are crucial in the wound healing process (Hidayat et al. 2018; Naghavi, Tamri & Asl 2021).

LC-MS/MS analysis identified Cinnamic acid ($C_9H_8O_2$) and Vanillin ($C_8H_8O_3$) at retention times of 7.44 and 7.21 min, respectively, with m/z values of 147.0444 and 151.0394 (Figure 1), aligning with findings by Silvi Ayu and Umar (2020), who reported concentrations of 16-26% cinnamic acid and <1% vanillin. These compounds are recognized for their significant roles in the potential pharmacological effects of the extract.

EMULGEL FORMULATION AND EVALUATION

Emulgel formulations were prepared using varying ratios of HPMC and Carbopol 940 were prepared, as follows: F1 (2.5:0.5), F2 (1.5:1.5), F3 (1:2), F4 (2:1), and F5 (0.5:2.5). Organoleptically, all formulas were yellowish-white with a semi-solid texture and a characteristic odor, meeting pH, adhesion, and emulsion type requirements. However, F3 and F5 exhibited coarse, non-uniform textures, failing homogeneity, spreadability, or viscosity criteria (Table 3).

Styrax benzoin ethanol extract resin has a very sticky texture, characterized by a hydrophobic nature. This hydrophobic component can be added into the oil phase of the emulsion base using emulgel preparation, facilitating the dispersion of oil globules into the water phase. In this study, the oil-in-water (o/w) emulsion type was selected to achieve easy application, minimal oiliness, and enhanced hydration. The selection of emulgators based on the required HLB value is also very important. This study used an emulgator concentration of 5% (HLB 12), with a combination of 2.65% Tween 80 (HLB 15.0) and 2.35% Span 20 (HLB 8.6) to form a stable oil-in-water (o/w) emulsion. HPMC and Carbopol 940 were combined in different ratios (0.5-2.5%) to optimize drug diffusion, texture, spreadability and viscosity (Iin Lidia, Anggun & Devi Hartianti 2019; Wiyono, Lestari & Wardani 2022).

Formulations F1, F2, and F4 met all evaluation criteria, whereas F3 and F5 exhibited coarser textures, paler colors, and higher densities, likely due to the increased concentration of Carbopol 940 (Dino & Sri Septyan Ayu 2017). This is consistent with previous studies that reported similar issues with higher concentrations of Carbopol 940, leading to thicker consistencies and granular textures in the preparation (Utami Wahyu, Jaka & Arsyik 2015). The denser texture of F3 and F5 resulted in low spreadability and high viscosity. These outcomes align with Erinda, Dewi and Dwi (2022), who found that higher concentrations of gel agents reduce spreadability and increase viscosity. Water evaporation during storage may have further contributed to viscosity increases (Erinda, Dewi & Dwi 2022; Utami

TABLE 2. Phytochemical analysis of *Styrax benzoin* ethanol extract

Phytochemical constituents	Test method	Test results
Flavonoids	$FeCl_3$ 5%	+
Saponins	foam	-
Alkaloids	Dragendorff's	+
Tannins	$FeCl_3$ 1%	+
Triterpenoids	$CH_3COOH + H_2SO_4$	+

+ indicates the presence; - indicates absence of phytochemicals

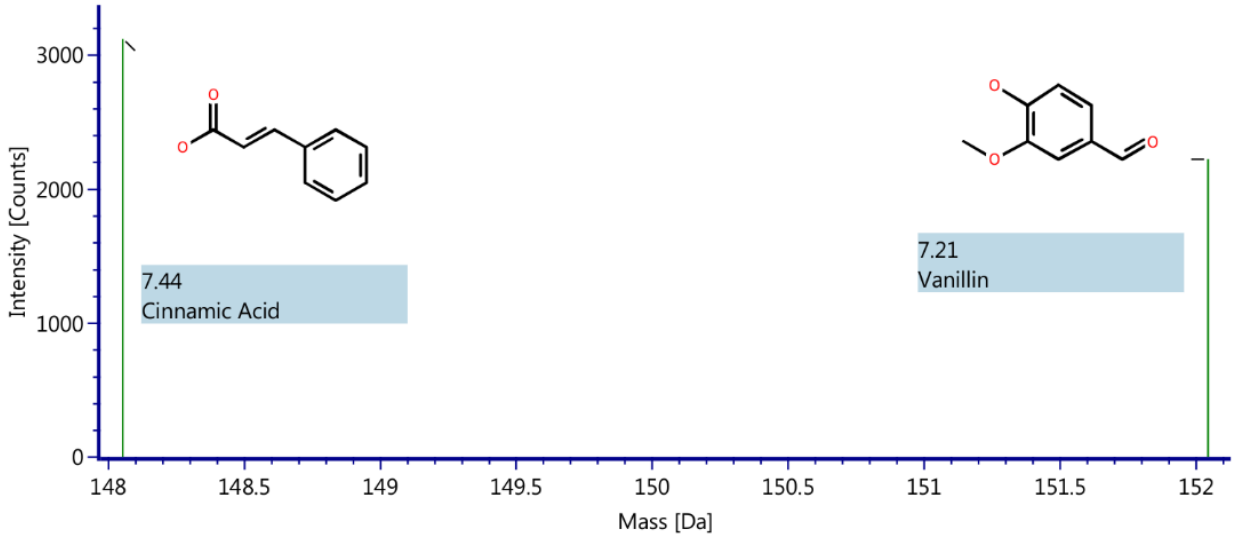


FIGURE 1. MS/MS spectra of *Styrax benzoin* ethanol extract

TABLE 3. Emulgel preparation evaluation data in formulas F1-F5

Formula (HPMC: Carbopol 940)	Homogeneity	pH (4,5-6,5)	Emulsion type	Spreadability (5 - 7 cm)	Adhesion (> 1 s)	Viscosity (2000 - 50000 cPs)
F1 (2.5% : 0.5%)	homogeneous	6	o/w	6.197 ± 0.25	5.900 ± 0.254	27391.7 ± 350.3
F2 (1.5% : 1.5%)	homogeneous	5	o/w	5.243 ± 0.281	4.573 ± 0.307	33308.3 ± 984.4
F3 (1% : 2%)	inhomogeneous	5	o/w	4.953 ± 0.137	3.867 ± 0.199	53550.0 ± 346.4
F4 (2% : 1%)	homogeneous	5	o/w	5.237 ± 0.031	4.310 ± 0.485	28266.7 ± 851.9
F5 (0.5% : 2.5%)	inhomogeneous	5	o/w	4.793 ± 0.215	3.58 ± 0.332	57666.7 ± 503.3

Wahyu, Jaka & Arsyik 2015). Arsiaty, Ilham and Fransiska (2020) and Faula Rohmatul, Landyyun Rahmawan and Fith Khaira (2022) also noted that stronger gel matrices, particularly with higher Carbopol 940 concentrations, lead to increased viscosity. Adhesion tests showed that F2 and F4 were the most stable, while F3 and F5 displayed an increase in adhesion, followed by a notable decrease in F1. Factors such as water evaporation, the addition of active substance concentration, other excipients, stirring method, temperature fluctuation, pH, and variations in particle size may have contributed to these changes (Erinda, Dewi & Dwi 2022; Naniek, Mimiek & Syarifatun 2012).

The stability test identified as F4, with a 2:1 ratio of HPMC to Carbopol 940, as the most stable formulation, consistent with findings by Fitra, Nanik and Nining (2021). Particle distribution analysis showed non-uniformity in size and shape, suggesting a poly-dispersed system. Over three months of storage at room temperature, the organoleptic properties (texture, color, odor) remained stable across all formulas. However, exhibited deteriorated homogeneity and increased off-white coloration.

The combination of HPMC and Carbopol 940 at a ratio of 2:1 (F4) was identified as the optimal formula based on desirability values close to one in spreadability, adhesion, and viscosity parameters (Table 2). This result was supported by the stability tests, which confirmed that F4 was the most stable formulation.

Based on the SLD method, the optimization equation for spreadability was Y = 5.90A + 4.67B, where A represents the concentration of HPMC and B is the concentration of Carbopol 940. The equation indicates that both agents positively influence spreadability, with HPMC having a stronger effect. For adhesion, the model equation was Y = 5.46A + 3.43B, again indicating HPMC as the dominant factor. For viscosity, the equation Y = 22869.99A + 57203.35B shows that both agents contribute to increasing viscosity, with Carbopol 940 playing a more significant role.

Following the identification of F4 as the optimal emulgel formulation, the preparation was evaluated for burn wound healing efficacy in mice. Emulgel preparations containing 1%, 5%, and 10% *Styrax benzoin* ethanol extract was tested. The 10% extract demonstrated the most effective wound healing, reducing the wound size from 2.316 ± 0.014 cm² on day 0 to 0.537 ± 0.012 cm² by day 15. The 5% emulgel showed a decrease from 2.686 ± 0.0123 cm² to 1.305 ± 0.015 cm², while the 1% emulgel reduced wound size from 2.332 ± 0.021 cm² to 1.196 ± 0.016 cm². In comparison, the negative control group exhibited a decrease from 2.069 ± 0.009 cm² to 1.091 ± 0.014 cm², and the positive control group (Bioplacenton®) from 2.146 ± 0.018 cm² to 0.921 ± 0.018 cm².

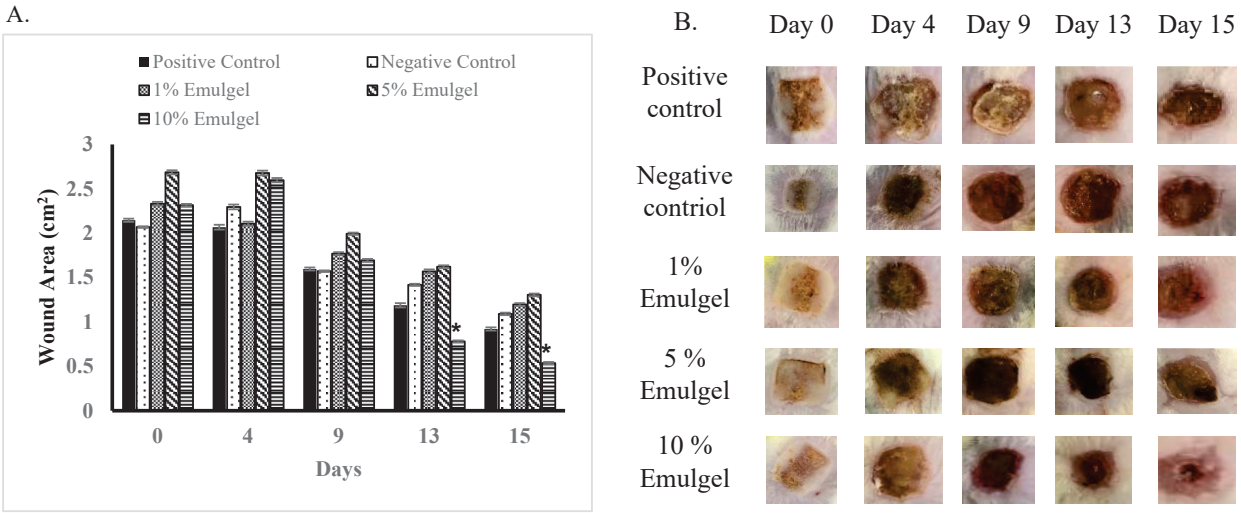
Statistical analysis using one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$) showed that only the 10% *S. benzoin* group had a significant difference compared to both the negative control and the 1% emulgel group. However, the 10% group did not differ significantly from the 5% group. Additionally, the 5% *S. benzoin* group and the positive control group did not show significant differences compared to any other groups. These findings suggest that while a higher concentration of *S. benzoin* (10%) provides optimal wound healing, the 5% formulation also yields comparable efficacy to the standard treatment and may offer a clinically relevant alternative.

Burn wound healing is a complex process that is divided into three phases: inflammation, proliferation, and maturation (Tuti et al. 2023). The inflammatory phase was clearly observed in the negative control group, where there was an enlargement of the wound area from day 0 to day 4 (Figure 2(B)). The inflammatory phase consists of homeostatic processes and phagocytosis (Cañedo-Dorantes & Cañedo-Ayala 2019; de Oliveira Gonzalez et al. 2016). In the homeostatic process, there was a reduction in bleeding due to vasoconstriction of vascular smooth muscle, caused by reflex mechanisms, the release of serotonin, thromboxane, and epinephrine by platelets broken based on rubbing against collagen on the surface of the injured blood vessel. In the process of hemostasis, platelet plug formation occurs due to the tearing of blood vessel endothelium, to facilitate contact with sub-endothelium collagen tissue to release ADP and thromboxane. Specifically, thromboxane functions as a binding agent between collagen and platelets in the wound area. This indicates that more production of ADP and thromboxane would result in greater platelets in the wound. The platelet plug in the wound blood is thicker and fibrin will strengthen the plug to enhance blood clotting. In the process of phagocytosis, vasodilation or changes occur in the cross-section of blood vessels resulting in increased blood flow around the wound. This vasodilation makes the wound area red and possibly enlarged, increasing the amount of blood in the wound and surrounding area to supply nutrients for the cells and macrophages. This additional blood also transports toxins produced by bacteria and dead tissue (Abdurrahmat 2014). Wound enlargement also occurred in the 10% emulgel group, yet the precise reason remains unclear as there have been insufficient studies regarding the toxic and optimal doses of *Styrax benzoin* ethanol extract for wound healing. Therefore, further investigation is required. Furthermore, in the proliferation phase, new blood vessel formation and burn wound healing occur, including re-epithelialization, granulation tissue formation, and collagen deposition in the burn area, resulting in the formation of reddish tissue containing blood vessels at the base of the wound. This process was observed after the fourth day, characterized by the presence of fibroblasts and no increase in wound area (Izzati 2015). During this phase, fibroblast cells and keratinocytes are activated by growth factors and cytokines, leading to the formation of granulation tissue and keratin in the wound area. Granulation tissue formation is influenced by angiogenesis, the formation of new blood vessels, and fibrogenesis. Specifically, fibrogenesis can cause the proliferation of fibroblast cells, resulting in thicker granulation tissue and faster wound closure (Izzati 2015; Riana Sari Puspita, Iche Andriyani & Subandrate 2020). The final stage is the remodeling or wound maturation phase, where inflammatory cells are absorbed, excessive collagen breakdown, advanced collagen formation, closure of new blood vessels, and wound contraction. Significant wound closure occurred in the 10% emulgel group with a reduction to 0.537 cm² ($p = 0.024$). The results of this study align with research by Izzati (2015) and Zakaria, Erviani and Soekendarsi (2021), which found that the highest wound healing percentages in consecutive order were 10% emulgel (75.83%) > positive control (56.35%) > 5% emulgel (51.21%) > 1% emulgel (48.80%) > negative control (47.28%).

The Styracaceae family, particularly the genus Styrax, has been studied for its potential in wound healing. The specific mechanisms are not fully understood, but the presence of these bioactive compounds suggests that they may enhance the body's natural healing processes.

This study found flavonoids, tannins, alkaloids, and triterpenoids as bioactive compounds in the ethanol extract of *Styrax benzoin* (Pauletti et al. 2006). Flavonoids act as antioxidants and influence inflammation by protecting cells from damage caused by prostaglandins and macrophages. They regulate key inflammatory molecules, aiding healing and showing potential in treating various inflammatory conditions, wound healing, and preventing invasion, angiogenesis, and metastasis. Flavonoids also strengthen collagen fibers, aiding wound closure. They are proposed for treating skin lesions with minimal topical side effects due to their lipophilic nature (Xia et al. 2023). Studies indicate that flavonoids decrease levels of inflammatory mediators like prostaglandins, leukotrienes, and cytokines such as IL-1β, TNF-α, IL-6, and IFN-γ. They also boost the production of anti-inflammatory mediators like interleukin 10 (IL-10), regulate nuclear factor kappa B (NF-κB) expression, and inhibit cyclooxygenase activity (Aliefia Ditha, Umi Kalsum & Ika Setyo 2015). Tannins facilitate healing by modulating diverse cellular mechanisms and growth factors. They exhibit antiproliferative properties, regulate free radical production, and contribute to limiting inflammatory processes. Alkaloids have been reported to modulate inflammation through the Nrf2 and AA pathways which help to regulate the body's natural response to injury. In addition, alkaloids also increase wound contraction rate and proliferation, which helps to accelerate the re-epithelization process (Fetse et al. 2014). Triterpenoids contribute to wound healing potential by promoting angiogenesis, enhancing cell proliferation and collagen synthesis, modulating inflammation, and exhibiting antimicrobial and antioxidant effects to prevent infection and oxidative damage to the healing tissue (Ghiulai et al. 2020). Cinnamic acid has been known as an anti-inflammatory agent, can prevent infection and stimulate wound healing, as well as histologically repair skin wounds (Naghavi, Tamri & Asl 2021). In addition, Vanillin, a phenolic compound, has anti-inflammatory, antioxidant, and antimicrobial effects (Du, Singh & Yi 2016). Thus, these findings emphasize that cinnamic acid and vanillin are the responsible compounds related to their activity in burn wound healing.

The positive control (Bioplacenton®), a commercial gel product widely used topically in Indonesia for burn wound treatment, was also compared for its effectiveness in this study. Its potential to reduce the burn wound area appeared lower than the 10% *Styrax benzoin* emulgel. Bioplacenton contains 10% placenta extract and 0.5% neomycin sulfate. The placenta extract stimulates new tissue formation, while neomycin sulfate is an antibiotic that prevents Gram-negative bacterial infection in wounds (Maharuni, Haryati & Andi 2019). Combining these two active ingredients is believed to provide faster wound-healing effects. However, the prolonged use of topical and systemic antibiotics on recovered wounds has resulted in major antibiotic resistance worldwide (Liu et al. 2020). The gel formulation of Bioplacenton also likely provides a delivery system similar to the *Styrax benzoin* emulgel formulated in this study. The percentage of burn wound healing in mice became stronger with increasing



Data were presented as mean ±SD (n = 4). The bar symbol represents the standard deviation. * = significantly different ($p<0.05$) from the negative control

FIGURE 2. Effects of Styrax benzoin emulgel in reducing burn wound area in mice (A). Graph of the decrease of burn wound area (cm2) in all treated groups on days 0, 4, 9, 13, and 15, and (B). Photographs of burn wounds area closure in all treated groups on days 0, 4, 9, 13, and 15

concentrations of *Styrax benzoin* ethanol extract in the emulgel (Figure 2(A)). This significant activity strength may be derived from the synergistic effects of several constituents of active compounds in *Styrax benzoin*. Several studies have reported that the synergistic effect involves the combination of different bioactive compounds that work together to enhance the healing process through various mechanisms, including antimicrobial and anti-inflammatory effects, enhanced cell proliferation and migration, antioxidant properties, and modulation of inflammatory response (Mitra et al. 2022; Nabilah et al. 2023). The presence of compounds such as cinnamic acid, vanillin, and triterpenoids provides antibacterial activity to address wound infections. Alkaloids, tannins, and flavonoids are believed to accelerate skin regeneration, facilitating faster wound healing. The findings in this study provide preliminary evidence to promote *Styrax benzoin* as a candidate for burn wound treatment. Moreover, the optimized emulgel formulation developed in this study holds potential for commercialization, although further research is necessary to fully establish its clinical applicability.

Several factors have shown a significant impact on the wound healing process. These included external factors such as contamination or infection. In contrast, internal factors were the immune system, tissue hypoxia, nutrition, and metabolic conditions of the animal (Arifah, Andi Evi & Eddy 2021; Theresia, Dyan Fitri & Umi Hanik 2022). This study also has limitations in assessing additional parameters of wound healing activity, including macroscopic and microscopic observations, histological analysis, and molecular-level mechanism confirmation testing. Hence, further experimental investigations are warranted in the future.

CONCLUSIONS

In conclusion, this study successfully formulated an optimal and stable emulgel preparation by combining gel agents between HPMC and carbopol 940 in a ratio of 2:1. This formula was also effective for burn wound healing, with the highest activity at 10% concentration of *Styrax benzoin* ethanol extract. However, understanding molecular wound healing mechanisms needs further confirmation.

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