A Systematic Review and Meta-Analysis of Biocellulose for Patients with Venous Leg Ulcers

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Abstract

1) *Introduction:* Among all vascular diseases, venous leg ulcers (VLU) are undeniably one of the leading causes of reduced quality of life and a significant medical burden. This condition requires prolonged treatment and wound management tools can be costly. Various dressing methods have been researched, yet till this date, no single dressing candidate has been found to fully meet all the criteria for an ideal wound dressing for VLU patients. 2) *Objectives*: This study aims to evaluate the effectiveness of biocellulose dressings in comparison to other existing dressings for VLU. 3) *Methodology*: A systematic search will be conducted across five databases (EMBASE, Cochrane Wounds Group Specialized Trials Register, PubMed, Scopus, and Thai Index Medicus) to identify all relevant data. 4) *Result:* A total of 113 studies were screened and nine studies were selected for data-extraction and analysis. Significantly, the pooled result for the meantime to achieve wound healing favored the biocellulose group, suggesting a faster healing time. Interestingly, the result for secondary outcomes did not show any significant differences, except for the superior ability of biocellulose dressings to alleviate pain and enhance hydration capacity compared to the control groups. 5) *Discussion:* To minimize bias, we aimed to include only randomized controlled trials (RCTs). While many outcomes showed minimal differences, at least three out of four studies favored biocellulose for reducing the time to re-epithelization. Although biocellulose offers convenience for patients with VLUs, its cost remains a concern. However, faster wound healing with biocellulose may reduce the overall number of applications, potentially improving patient's quality of life. 6) *Conclusions*: Biocellulose dressing is strongly recommended for VLU treatment due to its ability to accelerate wound healing, reduce the frequency of dressing changes, and alleviate pain, ultimately enhancing patients' quality of life. Although, its high cost is a concern, as long as it speeds up recovery and improves patients' quality of life, it should still be considered a viable treatment option for VLU patients.

Keywords: *wound dressing, wound healing, biocellulose, re-epithelization, venous leg ulcer*

1. Introduction

Among all vascular diseases, venous leg ulcers (VLU) are undeniably a significant cause of reduced quality of life and a major medical burden requiring prolonged treatment while wound management tools remain costly (Barnsbee et al., 2019; Guest et al., 2018; Philip et al., 2020). The annual medical care costs for patients with this condition in the United States range from $13,653 to $18,986 (Rice et al., 2014). This condition worsens in aging, obese, and sedentary populations (Davies, 2019). Traditionally, wound dressing management has involved using gauze soaked in a normal saline solution. Nevertheless, this type of dressing eventually dries out, causing adherence to the wound surface. Removing such dressing results in extreme pain and discomfort for patients (Numhom et al., 2017).

For this reason, various dressing methods have been researched to improve patients' quality of life. On the other hand, the standard management for VLUs includes compression bandages and direct wound care (Kirsner, & Vivas, 2015). Reducing leg swelling is essential for effective wound recovery (Gillespie et al., 2010). Even though compression therapy is the most practical approach, wound dressings that maintain adequate moisture also provide satisfactory results (Robles-Tenorio et al., 2022). The varying efficacy of different wound dressing methods can make it challenging for physicians to determine the optimal treatment choice.

With an interest in improving patients' quality of life through faster wound recovery, better wound hydration, fewer adverse effects, and a pain-free dressing removal process, biocellulose dressing has gained attention due to its advantages. Among all the dressing options for VLUs, biocellulose dressing is one of the newly invented techniques for wound management with varied data. Biocellulose is a gross chain of glucose synthesized by *Acetobactor xylinum* containing a nanostructure with high mechanical strength and moisture retention properties (Czaja et al., 2006). This unique composition displays remarkable efficacy in maintaining moisture and promoting wound healing (Czaja et al., 2006). Additionally, biocellulose dressings have been reported to provide instant pain relief, excellent absorbency, and rapid wound recovery from over 300 chronic ulcers and lesions reported (Fontana et al., 1990).

Farah (1986) and Ring's research in the 1980s was the first to document the use of biocellulose as a new element in wound care (Farah, 1986; Ring et al., 1984). Biosynthetic cellulose wound dressings have been reported to improve peri ulcer wounds which is superior to standard care (Dini et al., 2013). Dini and his colleagues suggested that biocellulose has a beneficial impact on the surrounding environment of cutaneous ulcers, promoting rapid wound restoration and enhancing the healing process. Although several studies have examined biocellulose dressing, there are still limited significant evidence regarding their efficacy for VLU patients, primarily due to small sample size (Gethin et al., 2015). Since biocellulose is well known for its ability to accelerate wound healing, maximize wound moisture, lessen undesired effect, and alleviate pain upon removal, we aim to evaluate its efficacy through a review study. As expected, to date, no systematic review or meta-analysis has been conducted on the efficacy of biocellulose dressings in VLU patients. Therefore, this study is conducted with the objective of reviewing the efficacy of biocellulose wound dressing compared to other moisture-retentive dressings in re-epithelization, and pain reduction.

2. Objectives

The objective of this study is to evaluate the efficacy of biocellulose dressing by comparing it with other types of existing dressings used for VLU management.

1) To assess the primary outcome which is the time required for wound healing.
2) To determine the secondary outcomes, such as ulcer area size reduction, time to achieve wound granulation, time to re-epithelization, quantity and quality of exudate, skin hydration, tissue color, side effects of the dressing, the degree of pain after dressing removal, and the impact of the dressing on infection rates. These secondary outcomes were selected not only because of their frequent reporting in most studies but also due to their importance in improving patients' quality of life.

3. Materials and Methods

This review will include all the criteria following the PICOS framework, with the population (P) focused on the patients with a reported history of existing venous leg ulcer conditions, including both unilateral and bilateral ulcers, as well as single and multiple ulcers. Intervention (I) included moisture retentive, antiseptic, and biocelullose dressings. Co-interventions will also be considered if they are administered equally across all trial intervention groups. Comparison (C) included other types of dressings for venous leg ulcers. Outcomes (O) comprise the primary and secondary outcomes. Lastly, study design (S) will primarily focus on randomized controlled trials (RTCs) due to their possibility to minimize potential biases.

Searches of five distinct databases (EMBASE, Cochrane Wounds Group Specialized Trials Register, PubMed, Scopus, and Thai index Medicus) will be conducted to identify all relevant data. These databases were selected based on accessibility through the Chulalongkorn University library with consultation from the university's librarian. The searches of the listed databases will cover studies on different timeframes (1963 until 2025). The key terms used in the search include biocellulose, venous leg ulcers, varicose ulcers, stasis ulcers, dressings, randomize control trials, prospective studies, or retrospective studies, which will be used interchangeably across the database.

After searching the distinct database, a list of articles was imported into the Covidence program, and two independent reviewers selected articles according to the eligible criteria. After filtering out duplicate articles, two independent reviewers preliminarily screened the titles/abstracts based on the inclusion criteria listed above. Duplicate records automatically filtered out by Covidence were excluded. Manual searches for duplicates were also conducted. The next step was to further screen the full-text articles to assess if the content matched the inclusion criteria. At this stage, Cohen's kappa statistical method was used to measure the inter-rater agreement between the two reviewers. Any remaining disagreements were resolved through consultation, review of the eligible criteria, consensus, and intervention from a third reviewer.

The data extraction was done using a data extraction template on Covidence platform. The extraction was conducted independently by two reviewers using a standardized form for the intervention review—RTCs, modified from the Cochrane Collaboration, with disagreements resolved through discussion or a third reviewer. Two main types of data were considered included dichotomous variables (odd ratio, risk ratio, or relative risk) and continuous variables (mean difference, confidence interval, p-value). The subgroup analyses were performed, and those data were interpreted using forest plots, funnel plots, and risk of bias analysis by RevMan 5.4.1. The risk of bias was assessed using the Cochrane RoB2 tools for RTCs. Statistical heterogeneity was evaluated using the I^2 statistic. The heterogeneity of the studies was evaluated by using the inconsistency index (I^2) statistic and the chi-square test. The Mantel-Haenszel fixed-effect model was used if the studies would potentially be homogenous ($I^2 < 25\%$ and chi-square test > 0.1). If the I^2 statistic $> 50\%$ equal moderate heterogeneity, and $I^2 > 75\%$ equals high heterogeneity. High heterogeneity studies were assessed using the random-effects model in the subgroup analysis. Furthermore, if missing data or outcomes were encountered during the data collection process, several attempts to contact the original authors, recalculation, and analyzing existing data were applied.

4. Results and Discussion

A total of 113 studies were screened using the Covidence platform. Among them, 43 duplicate references were automatically removed, and one additional duplicate was identified and manually excluded. This left 69 studies for further screening. Based on the inclusion and exclusion criteria, 58 studies were deemed irrelevant and excluded after reviewing their titles and abstracts. Only 11 studies were selected for retrieval and underwent a full-text review to assess their eligibility. Plus, Cohen's kappa statistical method was used to measure the inter-rater agreement between the two reviewers, resulting in substantial agreement ($\kappa = 0.65$). Of these, three studies were excluded for various reasons. Ultimately, nine studies were finalized for data extraction and analysis (Figure 1).

Basic Characteristic of the Studies

All studies were randomized in controlled trials (RCTs) published between 2004 and 2021. A total of 379 participants were enrolled, with 213 assigned to the experimental group (biocellulose) and 166 to the control group. All wounds were venous leg ulcers, and treatment durations ranged from 28 days (4 weeks) to 168 days (24 weeks). Most studies were conducted in Brazil, except for Alvarez et al.'s (2012) study in the United States and Slezak et al.'s study in Poland (Alvarez et al., 2012; Slezak et al., 2004). Notably, the study by Slezak et al. (2004) included three comparison groups, two of which (n=31) were part of the same experimental group but were stratified based on ulcer size. Compression therapy was used in all comparison groups, except those in the studies by Slezak et al. (2004) and Wild et al. (2010). Regarding follow-up visits, only Colenci et al.'s (2019) study implemented monthly follow-ups (Colenci et al., 2019). The control groups included petrolatum emulsion-impregnated cellulose acetate gauze, triglyceride oil, collagenase dressing, foam dressing, compression therapy, cellulose acetate mesh impregnated with essential fatty acids, hydrocolloid, and hydrofiber dressing in combination with zinc cream.

Primary Outcome: Wound Healing Time

As the primary outcome, the average time to achieve wound recovery was displayed by a forest plot based on the result of mean differences (MD). A random-effects model was used due to the high level of heterogeneity ($I^2 = 95\%$). The pooled MD was -15.76 days (95% CI: -29.79 to -1.73), indicating that biocellulose dressing significantly reduced the time to wound healing compared to the control group. The negative value suggests faster healing with biocellulose. While the result is statistically significant, substantial heterogeneity was observed among the included studies. Notably, the studies by Dini et al. (2012) and Silva et al. (2021) favored the control group (Figure 2). The result indicated that the difference in wound healing time between the biocellulose and control groups is not consistent across the studies. These findings might be due to several factors such as ulcer characteristics, ulcer severity, and treatment protocols that contributed to the variability. Despite showing a significant overall effect (P = 0.03) favoring biocellulose, the high heterogeneity weakens the confidence in applying these findings universally to all VLU patients. In clinical practice, wound healing time may vary greatly depending on patient-specific factors, making it difficult to generalize the results.

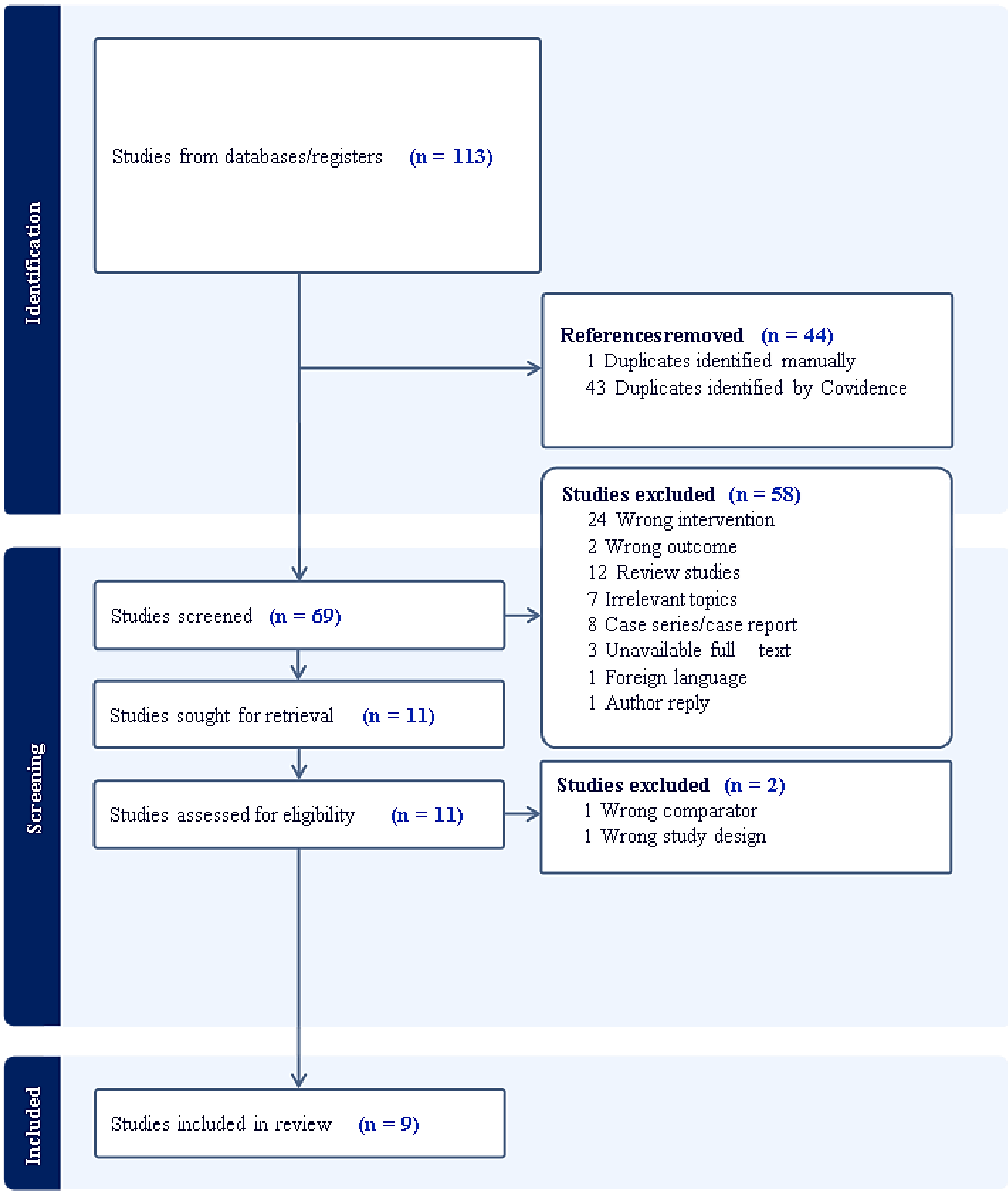

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) generated by Covidence.

Table 1: Basic characteristics of the eligible studies included.

Author	**Alvarez et al. (2004)**	**Alvarez et al. (2012)**	**Cavalcanti et al. (2017)**	**Colenci et al. (2019)**	**Dini et al. (2013)**	**de Barros Nunes et al. (2019)**	**Silva et al. (2021)**	**Slezak et al. (2004)**	**Wild et al. (2010)**
Year	2004	2012	2017	2019	2012	2019	2021	2004	2010
Country	United States	United States	Brazil	Brazil	NA	Brazil	Brazil	Poland	NA
Study design	RCTs	RCTs	RCTs	RCTs	RCTs	RCTs	RCTs	RCTs	RCTs
Experimental dressing	BC	BC	BC	BC	BC & Foam	BC	BC	BC	BC
Control dressing	Modified Unna's boot	Petrolatum emulsion - impregnated cellulose acetate	Triglyceride oil	Collagenase	Foam	Compression therapy alone	Cellulose acetate mesh impregnated with essential fatty acids	Hydrocolloid	Hydrofiber& Zinc cream
Secondary dressing	Compression therapy	Compression therapy	Gauze and elastic cotton bandage	Grade II compression therapy (23-32mmHg)	Grade IV compression therapy (45-55mmHg)	Grade III compression therapy (34-46mmHg)	Gauze and elastic cotton bandage	NA	Film or foam dressing
Sample size E/C	12/12	25/23	14/11	25/21	26/20	14/14	27/26	31/31/31	20/20
Wound etiology	VLU	VLU	VLU	VLU	VLU	VLU	VLU	VLU	VLU
Dressing changes frequency	Weekly	Weekly	Weekly	Daily	Weekly	Weekly	48-72 hours	Weekly	48-72 hours
Study period	84 days	84 days	120 days	90 days	28 days	168 days	180 days	12 months	28 days
Treatment duration	84 days	84 days	120 days	90 days	84 days	168 days	180 days	126 days	28 days
Follow-up period	Weekly	Weekly	Weekly	Monthly	Weekly	Weekly	Weekly	Weekly	Weekly
Ulcer inclusion criteria	VLU duration at least 2 months onwards	VLU duration at least 2 months onwards	VLU of CEAP 6, with or without contamination	Minimum evolution time of 6 weeks with a maximum of 20cm	VLU duration at least 2 months onwards till 6 months	VLU with an upper limit <90 cm^2	NA	NA	If there are bilateral ulcers, the largest ulcer will be used as the study reference

Study or Subgroup	Biocellulose Mean [days]	Biocellulose SD [days]	Biocellulose Total	Control Mean [days]	Control SD [days]	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alvarez et al. 2004	57	10	12	85	15	12	16.4%	-28.00 [-38.20, -17.80]
Alvarez et al. 2012	36	8	25	50	9	23	17.6%	-14.00 [-18.83, -9.17]
Colenci et. al 2019	60	9	25	90	12	21	17.3%	-30.00 [-36.23, -23.77]
Dini et al. 2012	84	15	26	83	12	20	17.0%	1.00 [-6.80, 8.80]
Silva et al. 2021	180	23	27	160	25	26	15.6%	20.00 [7.05, 32.95]
Slezak et al. 2004	84	25	31	126	18	31	16.2%	-42.00 [-52.84, -31.16]
Total (95% CI)			**146**			**133**	**100.0%**	**-15.76 [-29.79, -1.73]**

Heterogeneity: Tau² = 285.82; Chi² = 94.91, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.20 (P = 0.03)

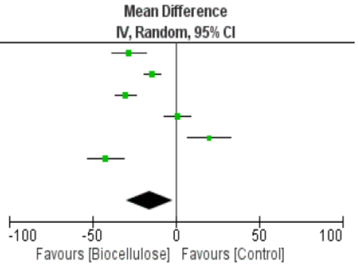

Figure 2 Forest plot of the average time required to achieve wound recovery.

Secondary Outcome

Ulcer Area Size Reduction

As the secondary outcome, ulcer area size reduction was measured at various time points. The mean difference (MD) was 0.46, suggesting a slight preference for biocellulose; however, there is substantial heterogeneity ($I^2 = 80\%$, $p < 0.05$). Despite this, there was no definitive evidence of a difference between the two groups, as the confidence interval included zero (95% CI: -2.96 to 3.87). Overall, the meta-analysis did not demonstrate a statistically significant effect of biocellulose compared to the control group (Figure 3). The high heterogeneity of the findings may limit the strength of the clinical recommendation.

Study or Subgroup	Biocellulose Mean	Biocellulose SD	Biocellulose Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Calvalcanti et al. 2017	37.3	1.8	14	39.8	3.2	11	30.4%	-2.50 [-4.61, -0.39]
Colenci et. al 2019	6.46	3.36	25	3.36	1.89	21	32.2%	3.10 [1.55, 4.65]
Dini et al. 2012	8.6	10.7	26	26.2	39.3	20	3.4%	-17.60 [-35.31, 0.11]
Silva et al. 2021	31.06	45.28	27	17.67	31.19	26	2.5%	13.39 [-7.48, 34.26]
Slezak et al. 2004	33.83	4.06	31	31.84	3.82	31	30.9%	1.99 [0.03, 3.95]
Wild et al. 2010	30.98	50.86	20	51.72	80.84	20	0.7%	-20.74 [-62.60, 21.12]
Total (95% CI)			**143**			**129**	**100.0%**	**0.46 [-2.96, 3.87]**

Heterogeneity: Tau² = 8.81; Chi² = 24.83, df = 5 (P = 0.0001); I² = 80%
Test for overall effect: Z = 0.26 (P = 0.79)

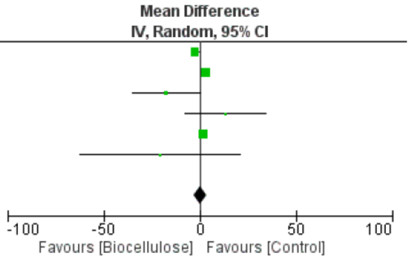

Figure 3 Forest plot of ulcer area size reduction at different time points compared to the baseline (initial assessment).

Time to Achieve Wound Granulation

Another secondary outcome was the time to achieve wound granulation. There was obvious heterogeneity across the observed studies (I^2=92%) due to inconsistency across the studies. It may be due to factors such as variation in wound treatment protocol across different dressing and biocellulose dressing application, or the different measurement methods for the wound granulation. All in all, the wound granulation time did not significantly differ much between the two study groups (MD=0) (Figure 4). In clinical practice, wound granulation time may vary broadly between different patients' groups, limiting the applicability of the findings across all settings.

Study or Subgroup	Biocellulose Mean	Biocellulose SD	Biocellulose Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alvarez et al. 2004	43	15	12	71	23	12	22.7%	-28.00 [-43.54, -12.46]
Alvarez et al. 2012	29.75	12.99	18	36.75	12.99	15	25.9%	-7.00 [-15.90, 1.90]
Calvalcanti et al. 2017	41.7	23	25	25	18	21	24.6%	16.70 [4.84, 28.56]
Wild et al. 2010	80.41	11.7	20	65.2	7.69	20	26.8%	15.21 [9.07, 21.35]
Total (95% CI)			**75**			**68**	**100.0%**	**0.00 [-17.51, 17.51]**

Heterogeneity: Tau² = 288.06; Chi² = 38.36, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.00 (P = 1.00)

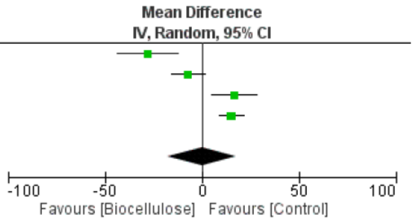

Figure 4 Forest plot of the time to achieve wound granulation.

Quantity and Quality of Exudate

Concerning quantity and quality of exudate, Alvarez et al., 2004 found that there were no marked differences between both groups. However, more effective exudate management was reported by the investigators in the biocellulose group (42%) compared with the control (22%) (p-value = 0.091 according to Alvarez et al., 2012). Moreover, according to Cavalcanti et al. (2017), the majority of the participants had little exudate; yet participant from the control group had little exudate (75%) at day 120 of the assessment, compared with the biocellulose group (66%). Furthermore, when we compared the moderate exudate between the participants of both groups, the control group still had more moderate exudate (24%) compared to the biocellulose group (8.3%). Colenci et al. (2019) mentioned there was no variation in exudate over time (p-value = 0.13). Lastly, Silva et al. (2021), the biocellulose group (33.3%) tended to yield more exudate compared to the control group (23.1%) at day 180. Additionally, the biocellulose group (59.3%) tended to yield more serosanguineous exudate compared to the control group (35.8%), although the finding was not statistically significant (p-value = 0.390).

Skin Hydration

For skin hydration, only one study of Dini et al., (2013) described that skin hydration assessed in the periulcer skin using corneometry showed a rapid and significant increase in the control group, where there was more presence of maceration. Meanwhile, the biocellulose group showed a more gradual and slower increase between day 14 and 18 (p-value = 0.001).

Tissue Color

Additionally, Calvacanti et al. (2017) found that the majority of the VLUs' tissue color was red (75%) compared to the biocellulose group (50%), while Dini et al. (2013) found that the inflammation and redness had reduced for both the experimental group (biocellulose) and the control group. However, there was a larger reduction for the biocellulose group on day 7 (p-value = 0.024), day 56 (p-value = 0.07), and day 84 (p-value = 0.006) (Mann-Whitney). At the same time, Silva et al. (2021) also found a similar outcome related to the redness of the wound after the dressings, with the biocellulose group (44.4%), and the control group (50%), p-value = 0.905.

Adverse Reactions

Interestingly, only three studies reported data on the incidence of adverse reactions related to biocellulose and control treatment. The most commonly reported adverse reactions were clinically infected ulcers, cellulitis, urticaria, and dermatitis. Figure 5 shows, although not statistically significant, that biocellulose dressing yielded fewer side effects compared to the control groups. The potential homogeneity in this study indicates the reliability of the pooled estimates. This finding may be more applicable to broader clinical settings because the included studies provide consistent results.

	Biocellulose		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Alvarez et al. 2004	0	12	2	12	5.8%	0.20 [0.01, 3.77]
Alvarez et al. 2012	6	25	8	23	62.2%	0.69 [0.28, 1.69]
Colenci et. al 2019	4	21	4	21	32.0%	1.00 [0.29, 3.48]
Total (95% CI)		**58**		**56**	**100.0%**	**0.72 [0.36, 1.46]**
Total events	10		14			

Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

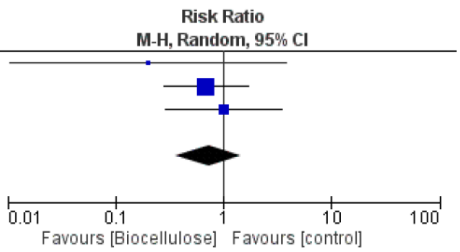

Figure 5: Forest plot of cutaneous side effects during the use of biocellulose dressings compared to the control groups.

Pain After Dressing Removal

Related to the pain after the dressing removal, Alvarez et al. (2004) found no marked differences between the two treatment groups. Meanwhile, a majority of patients in another study of Alvarez et al. (2012) reported significant results of no pain or mild pain during the dressing removal compared with the control group at each evaluation point (week1-12) (p-value < 0.05). Moreover, Cavalcanti et al. (2017) observed similar outcome related to the pain after the dressing removal. Study group who used biocellulose as the secondary dressing experienced lower pain measured by the Visual Analogue Scale (VAS). At the same time, Dini et al. (2013) found a significant pain reduction in the biocellulose group at 3 months of dressing application (p-value <0.0004). However, Colenci et al. (2019) and de Barros Nunes et al. (2019) found no difference observed between the two groups. Only the study of Wild et al. (2010) reported mean pain in dressing changes during the study period. The biocellulose group was reported to have mean pain of 2.25, 2.70, and 1.30 compared with mean pain score of the control group 3.73, 3.25, and 3.20 at day 7, 14, and 28 respectively. All in all, the majority of the study found significant reduction of pain during the dressing removal in the biocellulose group.

Impact of Dressing on the Infection Rate

On another note, none of the studies provided information on the bacterial clearance time of wounds. However, Cavalcanti et al. (2017) reported bacterial cultures obtained during the initial assessment. Both the control and biocellulose groups showed positive culture results. The biocellulose group had a higher prevalence of Pseudomonas aeruginosa (42.9%) compared to the control group (30%). In contrast, bacteria such as Providencia rettgeri (20%), Acinetobacter (10%), Proteus (10%), Escherichia coli (10%), Citrobacter (10%), and Providencia stuartii (10%) were more frequently isolated in the control group, with corresponding rates of 0%, 0%, 7.1%, 7.1%, 7.1%, and 0% in the biocellulose group. Meanwhile, the biocellulose group had higher rates of Staphylococcus sequorum (7.1%), gram-negative bacilli (14.4%), Staphylococcus aureus (7.1%), and Enterobacter (7.1%) compared to 0% in the control group. Overall, there was no significant difference in the bacterial culture results between the two groups.

Risk of Assessment and Publication Bias

According to Cochrane wound protocol (Higgins, & Green, 2008), most of the studies showed a low risk of bias in terms of random sequence generation (selection bias) and selective reporting (reporting bias). However, the study by Slezak et al. (2004) did not provide details about the participant selection method, making it unclear whether proper randomization was employed between the two comparison groups to reduce bias. Wild et al. (2010) appeared to have reported only significant and notable results related to biocellulose, which suggests potential reporting bias.

Although the majority of the studies reported using blinding methods, they largely failed to clarify whether allocation concealment was implemented for participants across groups. Notably, it seems nearly impossible to blind personnel in these studies, as randomization was conducted using open envelopes. This method would immediately reveal to the personnel assigning patients which group they belonged to. Additionally, four studies did not provide complete outcome data, which was inconsistent with their objectives. This may have been due to challenges such as loss of follow-up, which complicated the reporting of results aligned with the stated objectives. Furthermore, all studies were unclear about other types of biases beyond the commonly discussed ones summarized in Figure 6.

Failure to account for these biases could lead to an overestimation or underestimation of the biocellulose dressing's true effectiveness. Additional studies should incorporate rigorous methodologies, especially RCTs with appropriate blinding and comprehensive data reporting, to enhance the reliability of the evidence.

Concerning publication bias, the funnel plot was computed to evaluate the presence of publication bias related to complete wound healing. The result indicates that there is moderate symmetry within the plot. This suggests that there is moderate evidence of publication bias. The X axis represents the effect size, while the Y axis represents the standard error (SE) of the effect size. Larger studies with smaller SE are plotted near the top. In contrast, smaller studies with larger standard errors are plotted near the bottom. The dotted vertical line presents the overall effect size or null hypothesis (RR=1), while dashed triangular lines represent the region within which 95% of studies would be expected to fall in the absence of bias. In this case, most studies are clustered near the top of the funnel, indicating higher precision, while a few studies are further apart near the bottom, indicating greater variability (Figure 7).

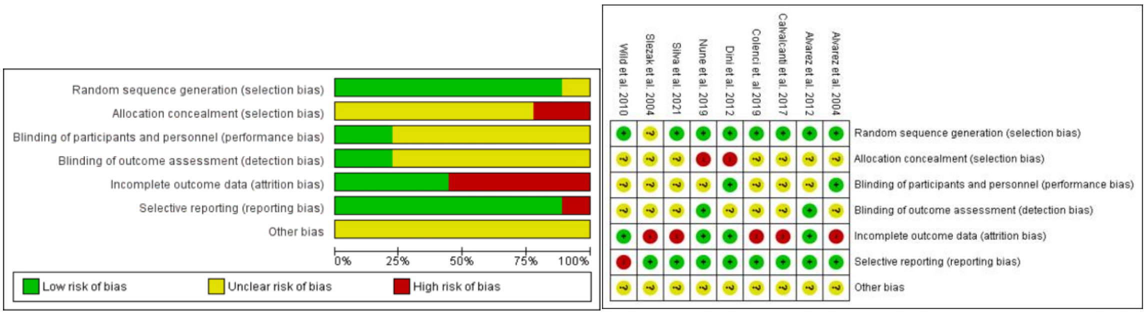

Figure 6 Risk of bias assessment computed by RevMan 5.4.1.

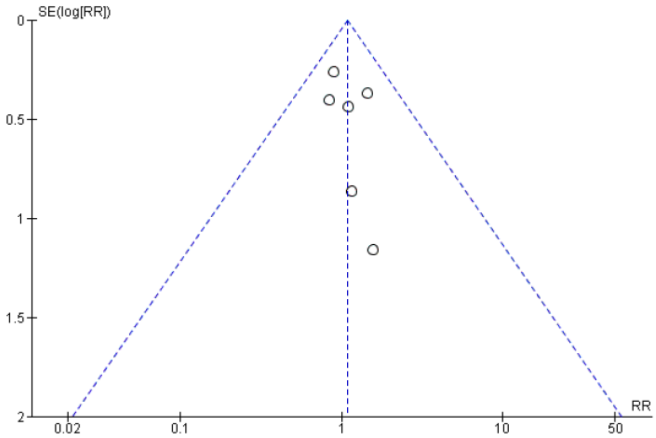

Figure 7 Funnel plot of complete wound healing.

5. Discussion

In today’s modern world, biocellulose dressing is one of the promising candidates for ulcer wounds due to its potential to retain moisture, and its compatibility with skin grafts (Momin et al., 2021). While clinical studies suggest potential benefits, the actual applicability depends on factors such as ease of application, patient preference, and healthcare costs.

In our study, we aimed to include only RCTs in order to minimize biases. However, the varying methods of recording results made it challenging to organize the dataset into a uniform structure. One of the main challenges during data collection was dealing with missing data. To address these issues, we applied several techniques recommended by the Cochrane Handbook (Higgins, & Green, 2008), including contacting the original authors, analyzing available data, inputting missing values, using statistical models to account for missing data, and making assumptions about their relationship to the existing data. The most significant difficulties included missing outcomes, summary data, individual-level data, and study-level characteristics required for subgroup analysis or meta-regression. Additionally, baseline-to-recovery data for many patients were either incompletely reported or inconsistently measured across studies. Another limitation was the small sample sizes inherent to RCTs, which led to some results being statistically insignificant. Furthermore, the risk of bias assessment and the publication biases showed the possibility of overestimation or the underestimation of biocellulose’s true efficacy due to certain biases found in the studies. This could be addressed by including more high-quality RCTs with low risks of biases and larger sample sizes. Moreover, the moderate evidence of publication bias suggested a potential overestimation of the treatment effect. If complete wound healing appears significantly faster with biocellulose, the clinician should be cautious before assuming the strong effectiveness of this dressing due to the presence of biases. The treatment decisions should be based on a combination of meta-analysis, clinical judgment, and high-quality RCTs.

Despite these challenges, we achieved significant findings regarding the primary outcome: the mean time to wound healing associated with biocellulose. Secondary outcome assessed various aspects of venous leg ulcers, including reduction in ulcer area, time to complete healing, granulation, re-epithelialization, exudate quantity and quality, skin hydration, tissue color, adverse reactions, pain during dressing removal, frequency of dressing changes, and bacterial clearance time. While many outcomes showed minimal differences, at least three out of four studies (Alvarez et al., 2004; Silva et al., 2021) favored biocellulose for reducing the time to re-epithelialization. Furthermore, (Alvarez et al., 2004, 2012) reported fewer adverse reactions with biocellulose compared to control groups. Biocellulose was also associated with significantly less pain, as it protected exposed nerve endings by sealing the wound from the external environment (Alvarez et al., 2012; Cavalcanti et al., 2017; Dini et al., 2013; Wild et al., 2010). From a patient-centered perspective, biocellulose has its advantages due to its cooling effect and the ability to reduce adherence to the wound bed, leading to less pain during the dressing change (Silva et al., 2021). This might be beneficial for the patients with VLUs, where frequent dressing changes may cause discomfort (Gethin et al., 2015).

Biocellulose's ability to create a protective, moist, and anoxic environment allows it to function similarly to a blister roof, shielding the wound. Additionally, it facilitates the dissolution of nonviable fibrin and enhances fibrinolysis under occlusive conditions (Alvarez et al., 2004). Silva et al., 2021 also noted a significant reduction in the frequency of dressing changes with biocellulose ($p = 0.001$), making it more convenient for patients and reducing the need for frequent wound cleaning, which can delay healing. Regarding bacterial clearance time, Cavalcanti et al. (2017) performed initial wound swab cultures but did not assess bacterial presence over time. This limits the ability to evaluate biocellulose's effectiveness in bacterial clearance. However, biocellulose itself lacks antibacterial properties unless combined with antiseptics like silver sulfadiazine or polyhexamethylene biguanide (Wild et al., 2010). Notably, ulcers that remain active or experience relapses are at a higher risk of infection, which can slow the healing process.

While biocellulose offers convenience for patients with venous leg ulcers, its cost is a concern. Colenci et al. (2019) reported that biocellulose dressings cost approximately $270 per month compared to $36 per month for collagenase. However, faster wound healing with biocellulose may reduce the overall number of applications, potentially improving patients' quality of life (de Barros Nunes et al., 2019). A cost-effectiveness analysis by Alvaro et al. (2018) found that biocellulose dressing reduced overall treatment costs in chronic wound management by shortening healing duration and minimizing complications (Patenaude et al., 2019). Nevertheless, their cost-effectiveness may vary depending on regional healthcare systems and policies. Lastly, it is important to emphasize the role of secondary dressing and compression therapy in accelerating wound healing, as highlighted in the literature. Almost all studies reviewed incorporated secondary dressings and compression, underscoring their significance in treatment. It is also absolutely crucial to educate patients on the acceptance and adherence to biocellulose-based treatment.

5. Conclusion

Managing venous leg ulcers (VLUs) presents significant challenges and necessitates appropriate wound dressings for effective treatment. The recovery period varies among individuals and can range from several months to years. Without proper treatment, VLUs can progress to severe complications, including amputation and other life-threatening conditions. Biocellulose dressings are strongly recommended for VLU treatment due to their ability to accelerate wound healing, reduce the frequency of dressing changes, and alleviate pain, ultimately enhancing patients' quality of life. Although the high cost is a concern, it speeds up recovery and improves patients' quality of life.

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7. References

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