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EFFICACY OF SNAIL MUCIN IN WOUND HEALING: A REVIEW

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Abstract

Snail mucin is a popular skincare ingredient in East Asia, as numerous studies and companies boast the healing potential of the ingredient. However, certainty of evidence regarding the efficacy of mucin as a topical treatment for various phases of wounds and burn healing are yet to be analyzed, therefore, a systematic review following the PRISMA guidelines was conducted to assess evidence regarding the efficacy of snail mucin in wound healing. PubMed and Google Scholar-listed studies comparing the healing potential of *Achatina fulica* and *Cornu aspersum* mucus to any comparator intervention in treating skin wounds were scanned to assess possible eligible studies for inclusion. Two review authors independently performed PRISMA items to assess the certainty of evidence. Nine studies matched the inclusion criteria and compared snail mucin to three patented drugs (MEBO, hydrocortisone, and SSD), collagen-based films, laser irradiation, and untreated samples. Snail mucin had significantly faster rates of burn surface epithelization and burn eschar detachment compared to MEBO. There was a slight improvement in burn wound closure favoring snail mucin compared to SSD. Snail slime and 1.5%

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chitosan had three times faster complete wound closure rate of ±1.2 days compared to hydrocortisone with incomplete wound healing at ±3.2 days. However, light irradiation recorded faster partial healing than snail mucin. Nonetheless, the certainty of the presented outcomes must be interpreted that the obtained evidence was from studies with low - very low certainty evidence, thereby limiting an inclusive conclusion to be formed. The data regarding snail mucin in wound healing is growing, but the body of evidence is still hampered by studies not following evidence-based standards, more appropriately reported RCTs may improve the certainty of evidence.

Index Term: *Achatina fulica,* Burns, *Cornu aspersum*, Glycosaminoglycans, Snail mucin, Snail secretion, Wounds

1. INTRODUCTION

Wounds are injuries that break the epithelial integrity of the skin or other body tissues and are accompanied by disrupted skin barrier function [1]. Immediate restoration of normal skin function is the goal of wound healing, a highly organized process that includes various phases and multiple growth factors occurring in proper order and time frame to restore epithelial integrity. Snail mucin is a popular ingredient in Asian beauty culture due to its skin-soothing and humectant properties. The mucin used for the cosmetic formulation is mostly composed of glycosaminoglycans (GAGs) [2],[3], hyaluronic acid [3], collagen [3], and elastin [3], which act as humectants and may potentially be beneficial for wound healing, inflammatory reduction, and anti-aging. *Cornu aspersum* and *Achatina fulica* are popularly used in the cosmetic industry due to their GAGs-rich chemical composition, which supports the skin structural protein collagen and elastin by drawing water into the different skin layers or by binding to copper peptides [4]. Other elements may include anti-inflammatory achasin [5], glycoconjugate for fibroblast proliferation, soothing allantoin [3],[6], and small amounts of glycolic acid [3],[6] for faster skin cell turnover.

Topical therapy is a dermatology practice that delivers drugs that benefit wound healing to the target site through topical applications. This is a versatile and useful treatment that minimizes side effects as no drug is being ingested and the possibility of harmful ingredients getting into the bloodstream is decreased, bringing satisfaction to the patient with a skin disorder. Snail mucin is a natural extract that has been studied tremendously over the years and is considered a treatment for disrupted skin barrier function by incorporating the secretions' humectant properties for wound healing. However, the certainty of evidence regarding the ability of snail mucin to aid various phases of wound healing as an effective topical intervention to result in faster wound healing is still ambiguous. Hence, this study aims to provide a systematic review of studies assessing the effects of topical administration of snail mucin from *A. fulica* and *C. aspersum* in wound healing. This systematic review followed the PRISMA guidelines along with clinical questions concerning PICOs to evaluate the certainty of the evidence of studies that assess the ability of snail mucin to induce faster wound healing, or a higher proportion of wounds completely healed.

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2. METHODOLOGY

A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1 Inclusion and Exclusion Criteria

Original articles assessing the efficacy of snail mucin from *Achatina fulica* and *Cornu aspersum* in wound healing were included, as studies with endpoints of evaluating the effectiveness of snail mucin or topical treatment that utilized 0.1-96% of snail mucin as an intervention treatment for wounds and burns were considered eligible for inclusion. Articles that are not in English, reviews, and studies assessing the antimicrobial property, anti-aging, anti-tumoral effect, and efficacy of mucin extracted from snail eggs alone were considered ineligible and were excluded.

2.2 Search Method

Databases PubMed and Google Scholar were searched from inception to May 2021 with key search terms: *Achatina fulica* or *Achatina fulica* mucin, *Helix aspersa* mucus, *Helix aspersa* and Mucin, *Cryptomphalus aspersa*, *Cornu aspersum* mucus, *Cornu aspersum* mucin, wound healing and snail mucin, snail mucin and wound healing, snail mucin and burns, snail slime burns, the search was duplicate-filtered and limited to studies reported in English.

2.3 Study Selection

Two authors independently assessed titles and abstracts for relevance and counter-verified by the other authors. Studies that matched the inclusion criteria were considered eligible and included in the review.

2.4 Data Extraction

Data extraction was conducted by one author and verified by the other author. Data extraction from each study included bibliometric indices, population characteristics, interventions, and outcomes.

2.5 Data Items

The clinical questions in association with PICOs are as follows

Participants/Population: People of any age with any type of wound or burn present on the skin. Animals as experimental models were eligible. Studies that conducted scratch assays. Wounds and burns not present on the skin were excluded.

Intervention: Studies that utilized topical therapy snail mucin and compared with any comparator interventions. Comparison: Comparison to standard care, placebo, untreated, or any comparator intervention.

Outcomes: Study outcomes did not form part of the selection process. The outcomes were structured into primary and secondary outcomes.

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Primary outcomes

- Time to complete the wound healing. Both the time to a wound healing event and the mean time to wound healing outcome were included.
- Change in wound surface area or proportion of the wound completely healed in a specific time period was included.

Secondary outcomes

- Pain
- Scar quality
- Patient satisfaction

2.5 Assessment of risk of bias in included studies

Cochranes Collaboration's risk of assessment tool was utilized to the assess risk of bias in individual randomized studies. Risk of Bias in Non- randomized Studies – of Interventions (ROBINS-I) was used to assess the risk of bias in non-randomized studies.

2.6 Outcome Measures

Time to complete wound healing or the proportion of the burn wound completely healed in a specified time period and the change in wound surface area or partial healing were considered primary outcomes of interest. Secondary outcomes of interest were pain reduction, scar quality, and patient satisfaction.

3. RESULTS AND DISCUSSION

3.1 Search Results

The search results are summarized in Figure 1. A total of 6,320 studies were identified in the initial conducted search via databases, and additional 198 studies were identified through the reference list of included studies. Nine articles matched the inclusion criteria and were considered eligible for inclusion in the review.

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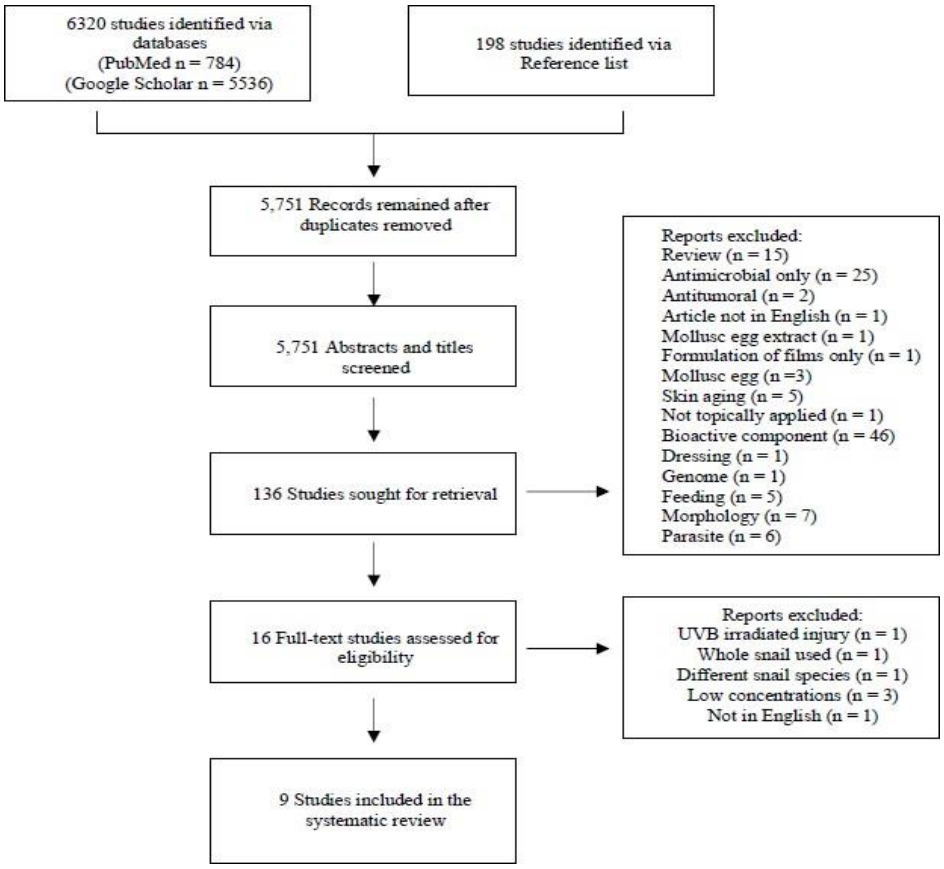

Fig. 1. PRISMA flowchart

3.2 Characteristics of Included Studies

The characteristics of the included studies are summarized in Table 1. All of the studies included provided a very low- to low certainty of evidence. The included randomized and non-randomized studies were undertaken in Indonesia [4],[7],[8], Brazil [9],[10], China [11], Bulgaria [12], Spain [13], and Greece [14]. Tsuotsos [14], Ledo [13], and their respective teams only included human patients with skin burns whilst, Song et al [11]. only included experimentally burned mice. The remaining studies [4],[8],[9],[10],[12] included rats inflicted with excisional wounds on the dorsal area. Only Putra and co-workers [7] included rats subjected to punch biopsy wounds on the dorsal region.

The included studies recruited 46 human patients with deep partial-thickness facial burns[13], 100 human patients with radiodermatitis burns[12], and 80 female Kunming mice with skin burn wounds [10]. The 228 rats were inflicted with excision wounds [4],[8],[9],[10],[112], and six Wistar rats were wounded through punch biopsy [7].

Only three studies compared the effectiveness of snail mucin to patented drugs MEBO [14], SSD [11], and hydrocortisone [4]. The other included studies compared the snail mucin to NaCl [4], collagen films [9], and water [11], and six studies compared the mucin to a control or untreated group [4],[7],[9],[10],[12],[13].

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Four of the nine studies included time to complete wound healing as a primary outcome of interest [4],[10],[11],[14]. Seven studies utilized the change in the proportion of the wound completely healed or partially healing as an outcome measure [7],[8],[9],[10],[11],[12],[13]. Secondary outcomes reported by the utilized studies included pain reduction [13],[14] and scar quality [9],[14]. None of the included studies reported on patient satisfaction.

Table 1: Characteristics of Included Studies

First author, year (Country of origin)	Number of participants (Male: Female) (Type of wound)	Anatomical area	Mean age (years)	Study Design	Intervention used	Outcomes (measures)	Results	
Tsuotsos, 2009 (Greece)	46 (25: 18) (Deep partial thickness facial burns)	Facial	47.05 (22-70)	Randomized Control Trial	MEBO VS Snail cream (Elicina 80% snail secretion filtrate)	Mean time for burn eschar detachment Burn surface epithelialization Post-intervention pain reduction	Snail mucin 9 ± 2 days 11 ± 2 days 2.70 ± 1.35	Comparator 11 ± 2 days 15 ± 2 days 2.00 ± 0.89
Harti, 2016 (Indonesia)	15 mice (Scratch) (Incision)	Back	-	Observational	NaCl VS Drug patent VS A1 VS A2 VS A3 VS A4 VS A5	Wound healing grade NaCl Drug Patent 1:2 snail slime & chitosan	GRADE 3.8 3.2 1.2	
Rosanto, 2021 (Indonesia)	Nine Wistar rats (Male) (Excision wound)	Back	3.5 months	Randomized trial	Control VS 24% 96% Snail gel	Angiogenesis per day of observation Day 2 Day 4 Day 7	CTR (Average) 2.6 10.6 11.6	96% (Average) 5.8 17.2 13.54
Kermedchiev, 2021 (Bulgaria)	24 Wistar Rats (Female) (Excision wound)	Dorsal thoracic region	205 g (Adult)	Observational	Control VS CERE 1	Wound contraction percentage Control CERE 1	Day 19 ~93% ~96%	
Ledo, (Spain)	100 (63:37) (Acute radiodermatitis)	Site or burn injury	59.09±12.81 years	Open, Controlled study	Control VS CAS gelcream	Rash Pruritus Burning	One week 22.16% 42.88% 48.48%	One month 54.78% 66.4% 87.87%
Santana, 2012 (Brazil)	100 *Rattus norvegicus* albinum (male)	Back	275 g	Randomized trial	Collagen VS Snail slime films	Collagen Deposition (21 days)	COL 44.76±0.11	Snail mucin 49.05±0.14
Song, 2021 (China)	80 Kunming mice (Female) (Burn wound)	Back	19 g	Randomized control trial	Snail mucus VS SSD	Burn wound healing (21 Days)	Mucus ~93%	SSD ~84%
Putra, 2021 (Indonesia)	Six Wistar Rats (Four punch biopsy wound)	Dorsal area	250-300 (275 g)	Observational	CMC-Na gel VS Snail mucin	Wound closure rate Day 7	CTRL 61.93±5.10	SM 96% 74.07±6.08
Santana, 2014 (Brazil)	80 *Rattus norvegicus* (Excision wound)	Back region	250-300 (275 g)	Randomized trial	Snail mucin VS LT VS ACHLT	Epithelialization rate (%) 21 Days	Snail mucin ~100%	LT ~100% ACHLT ~100%

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3.3 Risk of Bias in Included Studies

Figures 2 and 3 summarize and illustrate the authors' risk of bias assessment. The randomized studies by Rosanto [8], Santana [9],[10], and their colleagues recorded the highest risk of bias across all domains. The trials conducted by Tsuotsos et al. [14] had a lower risk of bias, whilst Song et al.'s [11] were judged least likely to be biased.

Three studies [8],[11],[14] were assessed to have a low risk of selection bias due to a detailed randomization procedure, although the remaining studies [9],[10] randomized participants into groups, and sequence generation was unclear. None of the included studies detailed the allocation concealment making it unclear whether trials were adequately concealed.

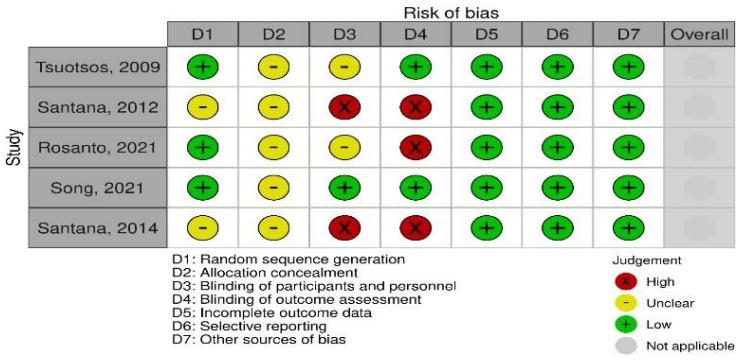

Figure 2: Review authors' judgment about each risk bias item for each randomized included study

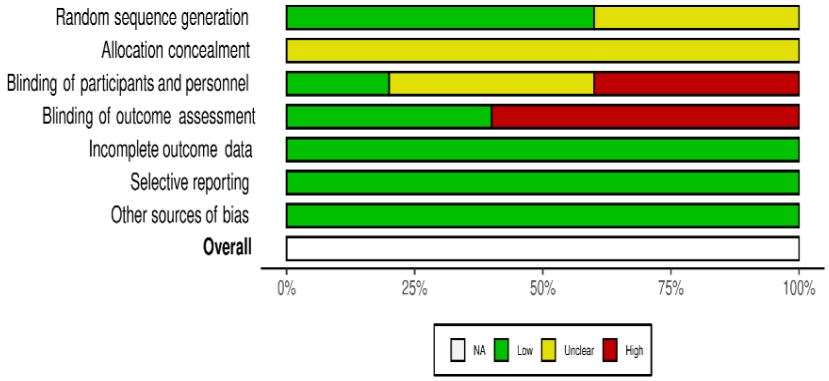

Figure 3: Review Authors' Risk of Bias Judgment Summary

Only Song et al. [11] detailed and implemented blinding of outcome assessors and patients and were judged least likely to be biased. The remaining trials were assessed to have an unclear and serious risk of bias. Due to a lack of blinding

Trials conducted by Santana et al. [9],[10] and Rosanto et al. [8] lack blind outcome assessment resulting in a high risk of detection bias. Tsuotsos et al. [14] and Song et al.

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[11] were assessed to have a low detection bias due to the blinding of outcome assessors.

All the studies were assessed to have a low risk of attrition bias due to either the complete presentation of data or the presentation of excluded participants. All included trials reported every precluded outcome and were judged to have a low risk of reporting bias.

Figures 4 and 5 summarizes and illustrate the authors' risk of bias assessment for non-randomized studies. All studies [4],[7],[12],[13] were assessed to have an overall high risk of bias due to a lack of blind outcome assessment.

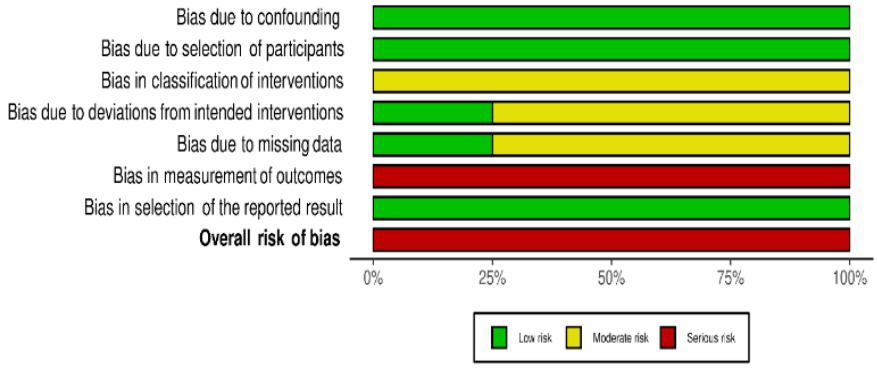

Figure 4: Review Authors' Judgment about Each Risk Bias Item for Each Non-Randomized Included Study

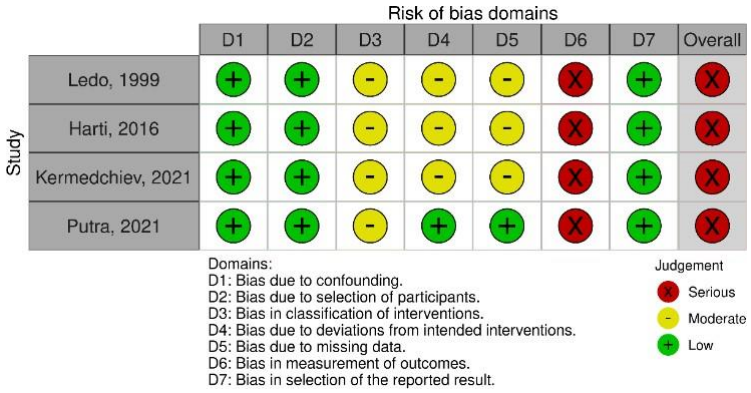

Figure 5: Review Authors' Risk of Bias Judgment Summary

3.4 Data Synthesis

A meta-analysis was precluded due to a high degree of heterogeneity, missing data, and poor-quality reporting from included studies. A narrative synthesis was performed to conclude the varied associated results.

3.4.1 Time to complete wound healing *(Primary outcome)*

Tsuotsos et al. [14] and Song et al. [11] observed faster burn wound healing in snail mucin treatment compared to MEBO and SSD, respectively. Tsuotsos et al. [10] observed a faster mean time of 9±2 days for burn eschar detachment compared to 11±2

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days of MEBO treatment. Additionally, patients with deep partial-thickness facial burns treated with snail mucin recorded a faster burn surface epithelialization within 14 days compared to MEBO (mean time for epithelialization: 11±2 days versus 15±3 days). Similarly, Song et al. [11] reported significantly higher rates of wound healing in the dorsal region of 80 mice with *A. fulica* mucus compared to the control, water, and SSD-treated groups. However, the obtained quantitative data regarding the wound-healing effect of the mucus was not reported.

Rats treated with the ratio of 1:2 of snail slime and 1.5% chitosan by Harti et al. [4] recorded optimum healing resulting in a wound is completely healed and dry compared to pharmaceutical-grade hydrocortisone with a wound partially healed (±1.2 days versus ±3.2 days).

Santana et al. [10] reported significantly higher epithelialization rates in rats treated with undressed laser irradiation and snail slime-dressed laser irradiation compared to control and mucus-only groups. However, no significant difference was observed in the effect of tested factors after a 100% epithelialization rate on the 21st day after treatment.

In summary, trials comparing the healing efficacy of snail mucin to MEBO, SSD, and hydrocortisone favored snail mucin. However, laser irradiation may provide a more rapid onset of the vascular phase of wound healing in comparison to snail mucin alone.

3.4.2 Proportion of wounds completely healed *(Primary outcome)*

Ledo et al. [13] observed faster healing of the clinical symptoms of radiodermatitis burns in patients treated with snail cream in comparison to the vehicle (Rash: 54.7% vs 31.7%; Pruritus: 66.4% vs 31.3%; Burning: 87.87% vs 47.3).

Both Santana [9] and Song et al. [11] observed a higher proportion of wounds healed through the surrogate way of inflammatory reduction. Santana et al. [9] recorded a more rapid granulation of tissue formation and fewer fluctuations in an inflammatory reaction in rats treated with snail mucin compared to collagen-based films. While in Song et al.'s study [11], mice treated with snail mucin recorded the lowest number of inflammatory biomarkers IL-6 and MAD compared to water and SSD. Harti et al. [4] reported that these improvements in time wound healing is due to the anti-inflammatory effect of acharan sulfate in *A. fulica* mucin. However, Santana et al. [9] reported that laser irradiation significantly reduced inflammation in relation to non-radiated groups (snail mucin and control) ($p<0.05$).

Rats treated with snail mucin by Rosanto [8] recorded a better proportion of wounds completely healed through a surrogate measure of angiogenesis. The treatment recorded the greatest number of blood vessels formed after seven days of treatment in comparison to the control (67 vs 58).

Collagen density was utilized as a surrogate way of partial healing, and both Santana [9] and Putra et al. [7] consistently favored snail mucin to induce the highest collagen density at the skin wound site of patients. Santana [10] reported that snail mucin induced higher collagen density at the wound site of treated rats compared to collagen-based films (49.05±0.14% vs 44.76±0.11%). Similarly, Putra [7] recorded higher collagen

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density in the 96% snail mucin-treated group compared to the control (48.81±5.29% vs 38.77±2.42%). However, Santana [10] favored laser irradiation over snail mucin (~90% vs ~59%).

When looking at epithelialization, both studies of Santana [9],[10] recorded no difference after complete epithelialization in snail mucin treatment, collagen-based films, and laser irradiation. Song et al. [11] reported that re-epithelialization occurred in both snail mucin and SSD treatment after 14 days.

Both Putra [7] and Kermedchiev et al. [12] recorded higher wound contraction rates in snail mucin treatment compared to the control. The mean wound contraction rate recorded by Putra et al. [7] for 96% snail mucin and control, respectively, were 74.07±6.08 % and 61.93±5.10

%. Kermedchiev et al.'s [12] patients with excision wounds treated with CERE 1 (snail mucin, plantain, and calendula extract) recorded a 61% higher wound contraction after six days of treatment compared to the control.

3.4.3 Pain, Scar Quality, and Patient Satisfaction *(Secondary Outcome)*

Two studies favored snail mucin in reducing the pain of patients with skin burn wounds. Ledo et al. [13] reported that snail mucin cream significantly reduced the burning sensation of patients with radiodermatitis burns compared to vehicle treatment (87.87% vs 47.3). In comparison to MEBO, Tsuotsos et al. [14] reported that snail mucin significantly reduced the pain score of patients compared to MEBO after intervention treatment (mean pain reduction: 2.70 ± 1.35 vs 2.00 ± 0.89).

While two studies did not favor snail mucin over comparator in ameliorating scar quality. Tsuotsos et al. [14] reported after a 2-year follow- up period that all patients in snail mucin and MEBO developed stable epithelial coverage after full surface epithelialization without scars. While Santana et al. [10] suggested that lower collagen deposition of snail mucin decreases the probability of hypertrophic scars and keloid formation.

None of the included studies reported patient satisfaction as an outcome measure.

3.5 Discussion

The results of the review should be interpreted with the following caveats in mind: there were various anatomical areas evaluated to assess the healing efficacy of snail mucin, the studies have very low to low certainty of the evidence, serious risk of bias from poor reporting, a high degree of heterogeneity precluding a meta-analysis be conducted, and the proportion of wound healing or partial healing was variously measured and reported such as reduction in inflammation, angiogenesis, collagen deposition, and epithelialization rate over time.

3.5.1 Time to Complete Wound Healing

Four studies reported time to complete wound healing [4],[10],[11],[14]. Three studies consistently favored snail mucin [4],[11],[14], while one favored laser irradiation [10]. Skin wound healing is composed of various phases that must occur in proper order and

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timeframe for the wound to completely heal. The final phase of wound healing may take up to a year or longer and may still lead to abnormal scar formation; hence, the use of topical interventions to support the well-coordinated process of wound healing is important to ensure skin integrity and normal skin barrier function.

Studies included in this review have consistently shown the efficacy of snail mucin in wound healing when compared to comparators hydrocortisone, MEBO, laser-irradiation, and SSD. Suggesting that Incorporating snail mucin in the proper ratio of formula and the use of the appropriate vehicle may subsequently deliver the properties of snail mucin to accelerate the time to complete wound healing. This outcome was in agreement with the earlier observations of Gentilli [15] and El-Zawawy [16], where wound healing utilizing cell scratch assays was completed at a shorter time in comparison to the control treatment. A faster onset of earlier phases of wound healing as reduction of inflammatory biomarkers, along with the production of growth factors and downregulation of metalloproteinase [15],[16] are common observations following topical application of snail mucin in the wound site. Even after scar formation and the matrix remodelling phase, snail mucin aids in the normal skin process, minimizing the possibility of forming scars and keloids [14].

3.5.2 Partial Healing

Three studies favored snail mucin compared to collagen-based films [9], pharmaceutical-grade hydrocortisone [4], and SSD [11]. Two of these were poorly reported, exposing them to significant biases. One study revealed that snail mucin might reduce fluctuations of inflammation more effectively than collagen-based films. Similarly, as reported by Song and co-workers, a small reduction in inflammatory markers IL-6 was significantly observed in snail mucin treatment compared to SSD. The study by Song et al. [11] was assessed to have a low risk of bias across almost all domains. The study that favors the comparator laser-irradiation [10] (LT and ACHLT) over snail mucin was poorly reported from a lack of blind outcome assessment and imprecision. These findings suggest that snail mucin may cause little improvement in wound healing time through a faster onset of the inflammatory phase and reduction of inflammatory biomarkers. Contrastingly, laser irradiation may cause little to no improvement in wound healing compared to snail mucin due to reduced fluctuations in inflammatory reaction. Similar anti- inflammatory activity of *C. aspersum* was reported by El-Zawawy [16], where the study reported the membrane stabilization of human red blood cells, albumin denaturation, and proteinase inhibitory activity of the land snail is comparable to aspirin.

Angiogenesis was improved by 96% snail mucin, producing the consistently greatest number of new blood vessels formed compared to the control treatment. However, Rosanto et al.'s [8] study was assessed to have very low certainty of evidence. Hence, there is no conclusive evidence that snail mucin may significantly stimulate endothelial cells to begin angiogenesis. Nonetheless, Rosanto et al.'s findings indicate that snail mucin may result in more favorable healing through the rapid onset of the proliferative phase by forming new blood vessels.

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Two of the three studies reporting on collagen deposition favored snail mucin compared to comparator treatments. Patients receiving snail mucin recorded the highest significant collagen deposition, compared to collagen-based film [9] and control treatments [7]. These results indicate that snail mucin has improved the collagen content in the wound site while simultaneously causing a more rapid replacement of type III for type I collagen compared to collagen-based films and control treatments. However, snail mucin coupled with laser irradiation may produce higher collagen content than snail mucin alone [10]. Collagen is a key factor in the wound-healing process and is a major compound of the extracellular matrix. Assembly and matrix remodeling is a pivotal step for fibroblast motility during wound healing and normal scar formation [2]. Higher collagen deposition after topical administration of snail mucin reported in this review [7],[8], is in agreement with previous studies [2],[18], where higher COL3A1 levels were observed [21] along with the downregulation of matrix metalloproteinases 1 and 2 expressions [2],[18]. Improvement of epithelialization from snail mucin was reported during the first 14-21 days of snail mucin treatment. Additionally, a higher wound contraction rate after snail mucin treatment was also consistently reported by included studies. As similarly reported by Gugliandolo

[18] on full-thickness excisional wounds in rats, topical administration of snail secretion caused an improvement in wound closure, granulation, and re-epithelialization, contributing to the overall restoration of the epidermis after 14 days of treatment in comparison to vehicle. Results of this review must be taken into context that the outcomes presented are from studies with low to very low certainty of evidence that consistently favor snail mucin in producing a shorter discharge rate in patients with facial burns [13], shorter time to complete wound healing [4],[11], a higher wound contraction rate [7],[12], more favorable effect in different phases of wound healing [13],[14], and better patient experience (pain reduction) [15] compared to various comparator topicals.

3.5.3 Secondary Outcome

Two studies with very low- to low certainty of evidence showed inconsistent results on pain reduction. Snail mucin may minimize the pain of patients with deep partial-thickness facial burns compared to MEBO [14] and cause little to no effect on the burning sensation of radiodermatitis burns [13].

In addition, low-certainty evidence from a single randomized trial does not favor snail mucin over MEBO in ameliorating scar quality after full burn epithelialization in patients with facial burns [14]. An assessment after a 2-year follow-up period indicating stable epithelial coverage of burn surface without scars in all patients is expected. Despite having low certainty of evidence and a low risk of bias, the results have reported the efficacy of snail cream comparable to MEBO- a more studied intervention.

Surgical films formulated with snail mucin and laser irradiation were reported to induce a moderate content of type I and type III collagen fibers [11]. However, laser irradiation alone replaced type III for type I collagen faster. The results of snail mucin films suggest a paced

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Production of collagen fibers for stable formation of scar quality rather than the former, which favors the overproduction of collagen, which may lead to hypertrophic scars and keloids. Because the certainty of the evidence is low to very low, this impedes any conclusion on the effect of snail mucin on pain reduction and scar quality. Our findings barely contribute to the body of evidence that favors the use of snail mucin over other topical agents in reducing pain and scar quality and enhancing patient satisfaction post-treatment. The objective of this systematic review was to assess the effectiveness of snail mucin in wound healing in people and animals with any type of wound or burn present on the skin. All topical interventions as comparators to mucus extract of *C. aspersum and A. fulica* were eligible for inclusion, and the reviewers identified a variety of topical agents to measure the efficacy of snail secretion in treating wounds. Participants were recruited from medical and laboratory institutions on three continents. Studies include most of the outcome measures, except for patient satisfaction. The evidence found after conducting this review is widely applicable and not restrictive to high-income countries because most snail mucin-based products are relatively cheap and available on the market. In addition, treatment of skin wounds and burn problems is not restricted to specialized medical and burn centers since at-home treatments using snail mucin topical agents are feasible and applied in the wound and burn care. The quality of evidence presented by the included studies is summarized in Table 2. The certainty of evidence combined in this review is mainly low to very low and is insufficient to draw a sound conclusion with a high degree of confidence.

Table 2: Summary of Findings

Snail mucin compared to comparator intervention for wound healing

Patient or population: Patient with wound or burn injury
Setting: Medical and Laboratory Institutions
Intervention: Snail mucin
Comparison: Any Comparator intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Snail mucin	Risk with comparator intervention				
Time for complete Wound healing (Tsuotsos, 2009)	The mean time for complete Wound healing was **11** days	mean **4 days higher** (1.87 higher to 12.15 higher)	-	46 (1 RCT)	⊕⊕◯◯ Low[a,b]	A cream containing *Cornu aspersum* mucin may slightly increase the proportion of burn wounds completely healed 14 days after treatment of deep-partial thickness facial burns, compared to MEBO
Proportion of wounds completely healed after 14 days (Tsuotsos, 2009)	**Low**		**RR 4.77** (1.87 to 12.15)	43 (1 RCT)	⊕⊕◯◯ Low[a,b]	Cream containing snail mucin produces slight increase in the proportion of wounds completely healed after 14 days of treatment compared to MEBO.
	270 per 1,000	**1000 per 1,000** (505 to 1,000)				
Wound closure rate or partial healing in 7 days (Putra, 2021)	The mean wound closure rate or partial healing in 7 days was **74.07 %**	mean **12.14 % fewer** (21.12 fewer to 3.16 fewer)	-	6 (1 observational study)	⊕◯◯◯ Very low[b,c]	*Achatina fulica* mucin may have little to no effect on wound contraction rate compared to control.
Collagen Deposition or Partial Healing (Santana, 2012)	The mean collagen Deposition or Partial Healing was **49.05 %**	mean **11.91 % lower** (11.99 lower to 11.83 lower)	-	40 (1 RCT)	⊕◯◯◯ Very low[b,c]	*Achatina fulica* mucin may have little to no effect on collagen deposition or partial healing compared to collagen films.

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Snail mucin compared to comparator intervention for wound healing

Patient or population: Patient with wound or burn injury
Setting: Medical and Laboratory Institutions
Intervention: Snail mucin
Comparison: Any Comparator intervention

Outcomes	Anticipated absolute effects* (95% CI) Risk with Snail mucin	Risk with comparator intervention	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Snail slime and chitosan in wound healing rate or Partial healing (Harti, 2016)	Snail slime and chitosan ratio of 1:2 showed the optimum outcome with a wound healing grade of ± 1.2 days, compared to the positive control of pharmaceutical-grade hydrocortisone with ± 3.2 days.			35 (1 observational study)	⊕◯◯◯ Very low[b,c]	The evidence is very uncertain about the effect of chitosan and snail slime on wound healing. There is very low certainty of evidence that 1:2 snail slime and chitosan healed wounds optimally than hydrocortisone.
Combined extracts with Regenerating effects on wound healing (Partial healing) (Kermedchiev, 2021)	CERE 1 (containing extract from *P. major*, *C. officinalis*, and mucus extract) exerted the best wound closure between the 3rd and 6th-day post-injury.			24 (1 observational)	⊕◯◯◯ Very low[b,c]	CERE 1 may have little to no effect on wound closure rate compared to control.
Angiogenesis and Partial Healing (Rosanto, 2021)	The greatest number of new blood vessels formed was observed on day four following the application of 96% snail mucus gel.			12 (1 RCT)	⊕◯◯◯ Very low[b,c]	It is uncertain whether 96% of snail mucin increases the rate of angiogenesis or wound healing compared to 24% and 48% mucus extract.
Epithelialization rate as measure of partial healing (Santana, 2014)	Laser irradiation and laser irradiation dressed with snail mucin were observed to have significantly higher epithelialization rates compared to snail mucin alone.			80 (1 RCT)	⊕◯◯◯ Very low[b,c,d,e]	Laser irradiation and laser irradiation dressed with snail mucin may have little to no increase in the epithelialization rate of wound healing compared to snail mucin alone.
Wound closure rate as measure of partial healing (Song, 2021)	The wound healing rate of SM group was significantly higher than that of SSD group.			80 (1 RCT)	⊕⊕◯◯ Low[a,b]	Snail mucin may accelerate the wound healing rate of burn injury compared to silver sulfadiazine.
Mean pain reduction (Tsuotsos, 2009)	The mean pain reduction was **2.70**	**mean 0.7 lower** (1.37 lower to 0.03 lower)	-	43 (1 RCT)	⊕⊕◯◯ Low[a,b]	It is uncertain whether snail mucin induces greater pain reduction compared to MEBO in facial burns as the certainty of the evidence is low.
Pain reduction (Ledo, 1999)	The mean pain reduction was **87.87 %**	**mean 87.87 % lower** (0 to 0)	-	100 (1 observational study)	⊕◯◯◯ Very low[b,c,e]	It is uncertain whether a cream containing *Cornu aspersum* mucin decreases the burning sensation of radiodermatitis burn compared to vehicle only.

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Patient or population: Patient with wound or burn injury
Setting: Medical and Laboratory Institutions
Intervention: Snail mucin
Comparison: Any Comparator intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Snail mucin	Risk with comparator intervention				
Scar quality (Tsuotsos, 2009)	All MEBO and Snail mucin treated patients formed stable epithelial coverage without scars			43 (1 RCT)	⊕⊕◯◯ Low[a,b]	MEBO and snail mucin may reduce the risk of scar formation for deep partial-thickness facial burns.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Unclear allocation concealment.
b. Downgraded for small sample size
c. Serious risk of bias due to the lack of blind outcome assessment.
d. Inconsistent outcome reported.
e. Used surrogate way of wound healing.

Potential bias in the review process might have arisen as a result of a lack of response to the review authors' queries from the authors of the included studies. The review authors tried to contact study authors via email to retrieve all possible quantitative data to assess the studies thoroughly- such as conducting a meta-analysis since the data available exhibits high heterogeneity. After about a month after the issued reminder, the review authors did not receive any response. Although Harti [4] initially responded, she did not provide any of the requested data as it was already deleted and deemed inaccessible. Only three studies [9],[13],[14] have statistical data available in the paper. The absence of another person in the review process to independently assess the study inclusion, risk of bias assessment, and data extraction may rise as another potential bias.

4. CONCLUSIONS

Snail mucin is a popular ingredient in the cosmetic industry due to its humectant and glycoprotein-rich component. Previous studies have reported the natural secretions from *A. fulica* and *C. aspersum* to reduce Tran's epidermal water loss, scavenge free radicals, reduce inflammatory biomarkers, increase collagen deposition, and downregulate metalloproteinase expression. All reported outcomes stemmed from studies with low to very low certainty of evidence on the efficacy of snail mucin in wound healing due to poor reporting and imprecision. Hence, the reviewers do not know with certainty whether snail mucin improves the time to complete wound healing or in aiding the various phases as part of partial wound healing when compared to collagen-based films, hydrocortisone, SSD, different mixtures of plant extracts, and control treatments. As observed in the faster healing after topical administration of snail mucin over comparator interventions,

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the reviewers assume that treatments with shorter time of discharge, higher wound contraction rate, and improvements in patient comfort, as observed in all snail mucin-treated patients across various studies may contribute to improved quality of care, patient satisfaction, and completion of treatment and may serve as a guide for health care providers. It is recommended for future studies to have a larger sample size, randomized trial participants into groups, and execute blinding in both participants and personnel to improve the quality of evidence.

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