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The Effect of Snail Mucus (*Achatina fulica*) on Wound Healing after Tooth Extraction: A Literature Review

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Abstract

Purpose: Tooth extraction is a frequently performed procedure within the field of dentistry, which results in a wound. The wound healing process can be enhanced by chemical and traditional medicines, one of which is snail mucus, which contains active compounds that play an important role in wound healing process. This study aims to further discuss regarding the effect of snail mucus on wound healing process after tooth extraction.

Methodology/approach: This literature review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines through PubMed, ProQuest, and Google Scholar database.

Results/findings: Snail mucus contains active compounds, such as protein, glycosaminoglycans, metal elements, allantoin, sulfates, calcium, mytimacin-AF, collagen, elastin, glycolic acid, hyaluronic acid, glutathione and vitamins which have effectiveness in enhancing the wound healing process with different mechanisms for each compound, both hemostasis, inflammation, proliferation, and remodeling processes.

Limitation: The limitation of this literature review is the lack of high-quality research. Furthermore, the lack of information on the specific doses of snail mucus used and the duration of treatment are critical difficulties that should be addressed in future research to allow for more comprehensive meta-analysis. Additionally, it is required to conduct testing and comparative analysis of the composition of snail mucus across other species in order to ascertain the efficacy of snail mucus content in species other than *Achatina fulica*.

Contribution: The results of this literature review are expected to be a reference in scientific development of wound treatment using traditional medicine, particularly snail mucus. Additionally, it is expected to increase the understanding regarding the effect of snail mucus on wound healing after tooth extraction.

Keywords: *snail mucus, tooth extraction, traditional medicine, wound healing*

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1. Introduction

Wound is a pathological condition characterized by the impairment or disturbance of the normal anatomical structure and physiological function. It can manifest as a rupture of the integrity of the skin epithelium or it can extend deeper into the subcutaneous tissue, causing damage to tendons, muscles, blood vessels, nerves, parenchymal organs, and bones (Velnar et al., 2009). A tooth extraction wound, the most commonly performed oral surgical procedure in dentistry, is an act of lifting or removing a tooth from the alveolus in the alveolar bone with various indications including dental caries, periodontal disease, necrosis pulpitis, pericoronitis, traumatic injuries, orthodontics, infections, cysts and tumors (Andersson et al., 2010; Langdon et al., 2011; Moore, 2011). When wound occurs on the body, including tooth extraction wound, physiological healing occurs by various biocellular and biochemical processes. The process of wound healing involves the complex biological process by which damaged tissue is regenerated to its normal tissue, involving the interaction of several cellular components, extracellular matrix (ECM), and a number of mediators, including growth factors and cytokines (Cañedo-Dorantes and Cañedo-Ayala, 2019; Gonzalez et al., 2016). Although wound healing is a natural process, the expeditious healing of wounds has significant importance for maintaining optimal health due to the fact that delayed wound healing can result in skin diseases, including edema and chronic ulcers (Choi et al., 2018). Several factors influence the process of wound healing, including age, hormonal fluctuations, stress levels, nutritional status, obesity, presence of systemic diseases, as well as the consumption of drugs, alcohol, and tobacco (Ilodigwe et al., 2012).

Povidone iodine is a frequently used pharmaceutical agent for the purpose of wound healing after tooth extraction procedures, which has a wide range of antimicrobial effects, even with brief exposure, and is categorized as a non-irritating antiseptic. However, it possesses corrosive properties that can lead to the rapid occurrence of severe chemical burns, as well as it has been associated with the development of hyperpigmentation within a two-hour timeframe (Gmur and Karpiński, 2020; Khan et al., 2023). Furthermore, the application of povidone iodine on tooth extraction wound can lead to several adverse effects, including pruritus, localized pain, inflammation, edema, and dermatitis (Putri and Ismardianita, 2016). The search should be directed towards identifying alternative pharmaceutical agent derived from traditional medicine. Traditional medicine products provide several advantages in comparison to modern clinical medications, including their little occurrence of adverse effects, affordability, simplicity, and widespread accessibility. According to the World Health Organization (WHO), traditional medicine encompasses a combination of knowledge, skill, and practices based on the theories, beliefs, and experiences specific to various cultures. These practices, regardless of their explicability, are employed for the purpose of promoting health, as well as preventing, diagnosing, ameliorating, or treating physical and mental ailments. Traditional medicine products include a diverse range of substances, such as herbs, herbal materials, animals, animal derivates, and minerals (World Health Organization, 2013).

Countries with tropical climates, such as Indonesia, have enormous natural potential to be explored and developed into phytopharmaca (Rosanto et al., 2022). The use of natural ingredients, such as various plants and animals, in traditional medicine has recently experienced a surge in popularity. Among these natural resources, snails have gained attention for their mucus, which contains active compounds that aid in the process of wound healing (Damayanti et al., 2020; Rosanto et al., 2021). Additionally, snails are an alternative treatment because they are easy to use, easy to find, have good skin spread ability, do not clog skin pores, have an antibacterial effect (Purnasari et al., 2012), and have been used extensively in human medicine and cosmetics (Zizioli et al., 2022). Several studies have provided scientific evidence indicating that the substances present in snail mucus have bioactivity that can effectively enhance the process of wound healing. The process of enhancement occurs in various phases, namely hemostasis, inflammation, proliferation, and remodeling. Therefore, the primary aim of this study was to explore the effect of snail mucus on the process of wound healing after tooth extraction, employing the methodology of literature review.

2. Literature Review

The wound healing process after tooth extraction is a physiological stage that begins with an inflammatory phase that lasts 2-3 days, at this stage, large numbers of inflammatory cells will move towards the socket area. Then proceed with the proliferative phase which lasts for about 2 weeks and is followed by the final phase, which is remodeling for about 1-3 months until the socket is closed again by the gingival tissue (Araújo et al., 2015; Mardiyantoro, 2018). In this study, we discussed the effectiveness of snail mucus in enhancing the wound healing process, including post-tooth extraction wound, because some evidence showed that snail mucus was effective in enhancing wound healing (Gugliandolo et al., 2021; Harti et al., 2016; Rosanto et al., 2021; Shoviantari et al., 2021; Suarni and Badri, 2016; Usman and Salikunna, 2015). This effectiveness is due to the contents in snail mucus. Snail (*Achatina fulica*) mucus contains active compounds, such as glycosaminoglycans (GAGs), proteins (hemocyanin, achacin, actin, cytoplasmic, and mucin), metal elements, allantoin, heparan sulfate, calcium, mytimacin-AF, collagen, elastin, glycolic acid, and hyaluronic acid (Deng et al., 2023; Waluga-Kozłowska et al., 2021).

3. Methodology

This literature review of published studies on the effect of snail mucus on wound healing after tooth extraction was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Systematic searches of the articles used were performed on several databases, including PubMed, ProQuest, and Google Scholar. In the literature search, several keywords were used, such as "snail mucus" combined with the keywords "wound healing" and/or "tooth extraction". The inclusion criteria included articles published within a period of 10 years (2013-2023) in Indonesian and English, primary research articles, and full-text articles. While the exclusion criteria included review articles and qualitative research. We identified relevant scientific publications in the database to review the literature. Furthermore, we evaluated and removed duplicate articles for further screening. We eliminated articles that only contain abstract for further analysis of article eligibility by only taking articles that discuss the effect of snail mucus on wound healing after tooth extraction. The last step was to review the articles that had been selected for further study in the discussion.

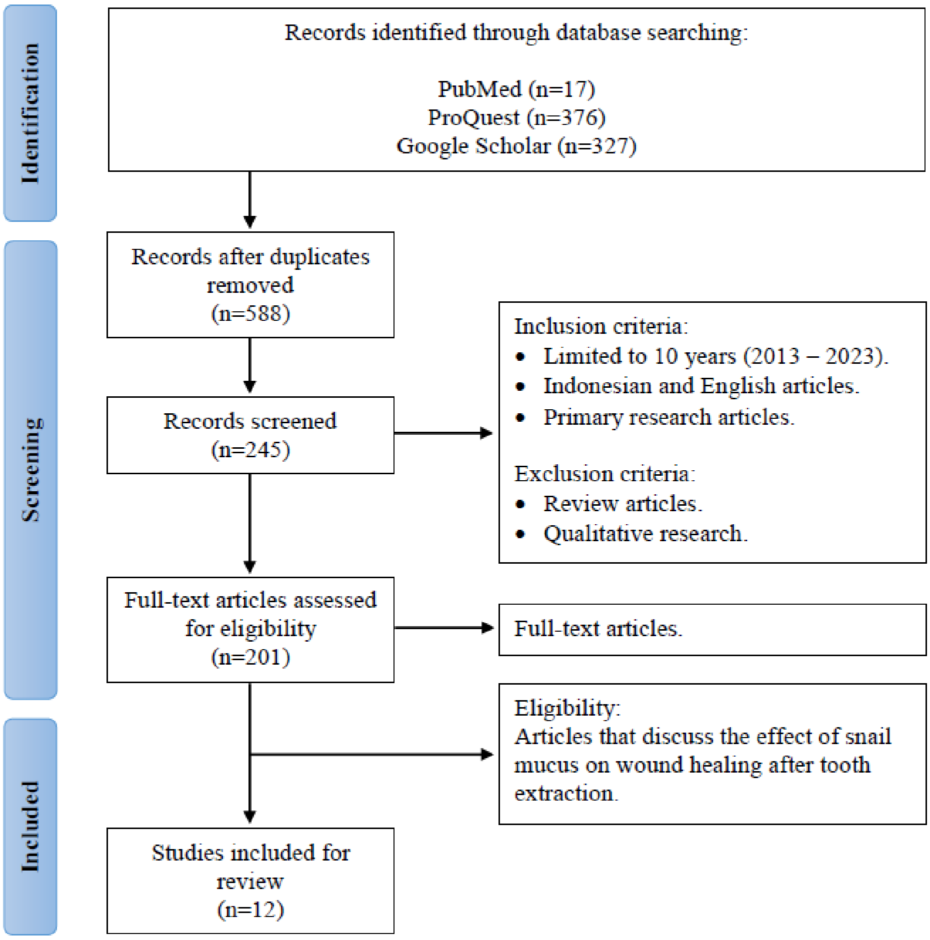

Figure 1. PRISMA flow diagram for the study selection process.

4. Results and Discussions

A total of 720 articles were identified from the database through the using of a combination of keywords. The titles were screened and the duplicates were removed, resulting in 588 remaining articles. The articles were subsequently screened based on predetermined criteria for inclusion and exclusion. After conducting a review that considered the inclusion and exclusion criteria, a total of 245 articles were screened. Then it was further filtered to only include the full-text articles, and a total of 201 full-text articles were further assessed for eligibility. After this selection process was completed, a total of 12 articles were included for the review.

Table 1. Summary of the included studies in the review.

No.	Researcher(s)	Title	Method	Results
1.	Yosaphat Bayu Rosanto, Cahya Yustisia Hasan, Rahardjo Rahardjo, Tri Wahyu Pangestiningsih (2021)	Effect of snail mucus on angiogenesis during wound healing	Experimental research using punch biopsy excision wound model in male Wistar rats	Test using a two-way ANOVA showed differences in the number of blood vessels formed. Turkey's HSD post hoc test showed that 24% snail mucus treatment had no effect on wound healing, but at concentrations of 48% and 96% showed a significant effect on angiogenesis. Therefore, it can be inferred that snail mucus has the potential to enhance angiogenesis.
2.	Nadya Jeihan Riyani, Robinson Pasaribu, Fredy Mardiyantoro (2021)	Evaluasi Jumlah Limfosit Pasca Aplikasi Lendir Bekicot (*Achatina fulica*) pada Soket Tikus Wistar (*Rattus norvegicus*)	Experimental research with the post-test only control group design using mandibular first incisor tooth extraction wound model in Wistar rats	The findings of the study indicated that there were differences in the number of lymphocytes on the third, fifth and seventh days. This study concluded that snail mucus had an influence on the lymphocytes count during the healing of tooth socket wounds in Wistar rats.
3.	Putu Sulistiawati Dewi, Setiawan DS (2020)	Lendir Bekicot Meningkatkan Jumlah Sel Makrofag pada Penyembuhan Luka Pasca Pencabutan Gigi Marmut	Experimental research using mandibular first incisor tooth extraction wound model in male guinea pigs	The findings indicated that the mean quantity of macrophage cells in the control group was 13.06, whereas in the treatment group it was 17.44 cells. The conclusion of the study showed that there was a significant difference in the number of macrophage cells in the two groups, therefore it may be inferred that the application of snail mucus has a positive impact on the proliferation of macrophage cells during the wound healing after tooth extraction.

4.	Tuo Deng, Dongxiu Gao, Xuemei Song, Zhipeng Zhou, Zhipeng Zhou, Lixiao Zhou, Maixian Tao, Zexiu Jiang, Lian Yang, Lan Luo, Ankun Zhou, Lin Hu, Hongbo Qin, Mingyi Wu (2023)	A natural biological adhesive from snail mucus for wound repair	Experimental research using L929 cell line, RAW264.7 cell line, and full-thickness skin wound model in normal and diabetic male rats	Snail slime can be used as a natural adhesive consisting of positively charged protein networks and polyanionic GAGs. The adhesive from snail mucus exhibited excellent hemostatic activity, biocompatibility and biodegradability, and was effective in accelerating full-thickness skin wound healing in normal and diabetic male rats. In addition, snail mucus effectively promotes macrophage polarization, relieves inflammation, and promotes epithelial regeneration and angiogenesis.
5.	Christal G. Oroh, Damajanty H. C. Pangemanan, Christy N. Mintjelungan (2015)	Efektivitas Lendir Bekicot (*Achatina fulica*) Terhadap Jumlah Sel Fibroblas pada Luka Pasca Pencabutan Gigi Tikus Wistar	Experimental research with the post-test only control group design using mandibular first incisor tooth extraction wound model in male Wistar rats	The results of the study stated that snail mucus had activity in increasing the number of fibroblast cells in the post-tooth extraction wounds of Wistar rats. The number of fibroblast cells in male Wistar rats that were administrated snail mucus was higher than in mice that were not given snail mucus.
6.	Agnes Sri Harti, S. Dwi Sulisetyawati, Atiek Murharyati, Meri Oktariani (2016)	The Effectiveness of Snail Slime and Chitosan in Wound Healing	Experimental research using incision wound model in mice	The results of the study indicated that snail mucus has several compounds that function in the process of wound healing, such as beta agglutinin, achacin protein, acharan sulfate and glycoconjugates. Additionally, snail mucus also contains active compounds such as isolate, heparan sulfate, and calcium. The compounds contained in snail mucus have antibacterial and anti-inflammatory effects so that the proliferation process will heal the wound immediately. Therefore, it can be inferred that snail mucus has effectiveness in the wound healing process, including tooth extraction scars.

7.	Fenita Shoviantari, Shofiatul Fajriyah, Ela Agustin, Shafia Khairani (2021)	Uji Aktivitas Gel Lendir Bekicot (*Achatina fulica*) Sebagai Penyembuhan Luka Sayat	Experimental research using incision wound model in male rats	The study findings showed that the application of snail mucus at a concentration of 10% shown efficacy in enhancing the wound healing process. In the process of wound healing, on the fifth day in group K (+) (wounds treated with bioplacenton) and group P1 (wounds treated with 10% snail mucus), there were several healing wounds which experienced a significant increase. In group P2 (wounds treated with 15% snail mucus) and P3 (wounds treated with 20% snail mucus) began to heal on the sixth day. Whereas in group P4 (wounds treated with 100% snail mucus) healed on the seventh day. And in the K (-) group (untreated wounds) the wounds had not shown any healing. The findings of this study showed that group P1 had the most effective wound healing activity, using snail mucus at a concentration of 10%.
8.	Ertati Suarni, Putri Rizki Amalia Badri (2016)	Uji Efektivitas Lendir Bekicot (*Achatina fulica*) Dibandingkan dengan Povidon Iodine 10% Terhadap Penyembuhan Luka Sayat (*Vulnus Scissum*) pada Mencit (*Mus musculus*)	Experimental research with the post-test only control group design using incision wound model in male Wistar rats	This study findings indicated that the average wound healing in distilled water administration was 9.83 ± 1.32 days, 10% povidone iodine administration was 6.83 ± 0.75 days, 100% snail mucus administration was 6.5 ± 1.64 days, administration of 75% snail mucus was 6 ± 1.26 days, and administration of 50% snail mucus was 6.16 ± 0.75 days. It can be concluded from the results of this study that administrating snail mucus is more effective in healing wounds compared to administrating aquadest. While the duration of wound healing in administration of snail mucus was not significantly different from that of 10% povidone iodine.

9.	Yosaphat B. Rosanto, Cahya Y. Hasan, Rahardjo, Antonius Surya (2022)	The Potential of Snail (*Achatina fulica*) Mucus Gel as a Phytopharmaca to Accelerate the Inflammation Process during Wound Healing	Experimental research using punch biopsy excision wound model in male Wistar rats	The findings of the study demonstrated a statistically significant increase in the quantity of polymorphonuclear (PMN) leukocytes on the second to fourth day with the highest number of PMN leukocytes found in the 96% snail mucus treatment group. The findings of this study suggest that the application of snail mucus has a notable impact on PMN leukocytes in the wound healing process.
10.	Abd Rachman Usman, Nur Asmar Salikunna (2015)	Pengaruh Lendir Bekicot (*Achatina fulica*) Terhadap Waktu Penutupan Luka Sayat (*Vulnus Scissum*) pada Mencit (*Mus musculus*)	Experimental research with the post-test only control group design using incision wound model in Wistar rats	The findings of the research study indicated that the application of snail mucus to wounds resulted in a more accelerated process of wound healing, with an average duration of 6.75 days. In contrast, wounds that did not get treatment with snail mucus showed an average wound closure time of 8.1 days.
11.	Alessia Ricci, Marialucia Gallorini, Nadine Feghali, Simone Sampò, Amelia Cataldi, Susi Zara (2023)	Snail Slime Extracted by a Cruelty Free Method Preserves Viability Controls Inflammation Occurrence: A Focus on Fibroblasts	Experimental research using HaCat cell line, CRL-9855 cell line, and human gingival fibroblasts (HGFs)	The study results proved that snail mucus can promote fibroblast viability and induce wound healing mechanisms by activating Erk protein. The anti-inflammatory effect of snail mucus is evidenced by the downregulation of COX-2 expression, whereas the induction of angiogenesis is supported by the upregulation of Ang1 gene expression and increased matrix deposition.
12.	Enrico Gugliandolo, Francesco Macri, Roberta Fusco, Rosalba Siracusa, Ramona D'Almico, Marika Cordaro, Alessio Filippo Peritore, Daniela Impellizzeri, Tiziana Genovese, Salvatore	The Protective Effect of Snail Secretion Filtrate in an Experimental Model of Excisional Wounds in Mice	Experimental research using punch biopsy excision wound model in male mice	The microscopic results of this study showed that administration of snail mucus significantly increased the speed and percentage of wound closure. Snail mucus promotes several markers of appropriate wound healing, such as collagen deposition (collagen type III alpha 1 (COL3A1), matrix metalloproteinases (MMPs)) and tissue remodeling processes (alpha-smooth

Cuzzocrea, Rosanna Di Paola, Patrizia Licata, Rosalia Crupi (2021)		muscle actin (α-SMA), vascular endothelial growth factor (VEGF)). In addition, snail mucus is indicated to inhibit the inflammatory process in wound tissue (myeloperoxidase (MPO), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α)).

Snail mucus has compounds that have benefits in enhancing the wound healing process, this is in accordance with the results of tests conducted by Deng et al. (2023) which stated that snail mucus contains protein (34.1%), GAGs (15.9%), metal elements (Ca^{2+} and Mg^{2+}), allantoin (2.65%), sulfate content (15.4%), and calcium (2.64%). The main protein content in snail mucus includes hemocyanin, achacin, actin, cytoplasmic, and mucin. Additionally, snail mucus also contains mytimacin-AF, collagen, elastin, glycolic acid, hyaluronic acid, glutathione, and vitamin A, groups B and E (Gugliandolo et al., 2021; Kermedchiev et al., 2021; Song et al., 2021; Trapella et al., 2018; Vassilev et al., 2020; Waluga-Kozłowska et al., 2021). However, the composition of snail mucus exhibits variations depending on factors such as snail species, role, and level of adhesion (Waluga-Kozłowska et al., 2021). In vitro cytotoxicity of snail mucus was also tested using the 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide (MTT) assay and it was found that snail mucus has no obvious effect on cell viability and its effect on the cell growth curve was unclear. According to the Standard Practice for Assessment of Hemolytic Properties of Materials, the hemolysis ratio of snail mucus in the hemolysis test was within the permitted range of less than 5% as a biological material. Activated partial thromboplastin time (APTT) testing of snail mucus showed that the content of GAGs such as heparin did not show APTT prolongation activity, so there was no risk of bleeding (Deng et al., 2023).

Wound healing begins with an initial inflammatory or hemostatic phase that occurs as a result of the body's response to attempting to stop bleeding by activating intrinsic and extrinsic coagulation factors, leading to platelet aggregation and clot formation vasoconstriction, shrinkage of the damaged vessel ends, and hemostatic reactions (Primadina et al., 2019). There are three coagulation processes that occur in the hemostasis phase, namely the formation of thromboplastin, activation of prothrombin to become thrombin, and the formation of fibrinogen to become fibrin. Beta agglutinin contained in snail mucus has a role in the formation of thromboplastin (Putra, 2015). Then, in this phase there will also be migration of lymphocytes and platelets to the injured tissue which is triggered by the activation of membrane-associated kinases which increases the permeability of cell membranes to Ca^{2+} ion and activates collagenase and elastase (Landén et al., 2016). Simultaneously, the injured tissue and platelets release cytokines which function to release inflammatory factors and various growth factors such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), VEGF, interleukin-1 (IL-1), insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), and chemokines (Andersson et al., 2010). In this phase, snail mucus has been tested for its effectiveness in blood clotting, and it was found that snail mucus accelerates blood clotting than gauze. The hemostatic effect test showed that the decrease in blood-clotting index (BCI) could be related to the strong adhesion of the snail mucus to the blood cells. In the bleeding model, the negative control group had a blood loss of 238.2 ± 24.90 mg, the group with gauze which did not have a significant hemostatic effect of 213.0 ± 46.06 mg, while the snail mucus administration showed a blood loss of 113.0 ± 17.16 mg. Snail mucus can absorb liquid quickly and form an adhesive hydrogel at the bleeding site (Deng et al., 2023). This is due to the isolate content which functions as an antibacterial and analgesic (Harti et al., 2016; Riyani et al., 2021), as well as heparan sulfate and calcium which play a role in the process of hemostasis (Kesumaningrum and Indriyanti, 2021).

After hemostasis is accomplished, acute inflammatory cells and neutrophils will infiltrate the inflammatory area and destroy all debris and bacteria, in this process enhanced by GAGs containing heparan sulfate in the snail mucus (Olczyk et al., 2015). This is in accordance with a study conducted by Rosanto et al. (2021) which stated that on the second day, wound treated with snail mucus showed tissue filled with inflammatory cells without surface epithelium. Neutrophils will secrete pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and proteases to degrade the remaining ECM. Furthermore, monocytes differentiate into macrophages into the wound through monocyte chemoattractant protein-1 (MCP-1) mediation (Primadina et al., 2019). When macrophages are activated, they release growth factors and cytokines, such as transforming growth factor-alpha (TGF-α), transforming growth factor beta-1 (TGF-β1), PDGF, IGF-1, IGF-2, TNF-α, and IL-1 (Miloro et al., 2011). Wound treated with snail mucus had a high number of macrophage cells, the results of testing the number of macrophage cells in the control group using CMC-Na 2% gel was 13.06 cells, whereas in wound given snail mucus had an average number of macrophage cells as many as 17.44 cells, this shows that the application of snail mucus is more efficacious in promoting the proliferation of macrophages cells during the wound healing process after tooth extraction (Dewi and DS, 2020).

The efficacy of bacterial destruction during the inflammatory phase is enhanced by several compounds in snail mucus, such as mucin which contains antibacterial proteins that exhibit activity against both gram-positive and gram-negative bacteria (Riyani et al., 2021; Waluga-Kozłowska et al., 2021), mytimacin-AF peptide with antibacterial and antifungal activities, and achacin glycoprotein which has antibacterial activity which shows L-amino acid oxidase activity and can produce cytotoxic hydrogen peroxide and is able to damage the bacterial cytoplasmic membrane so that bacteria cannot undergo cell division (Anggraeni, 2018; Waluga-Kozłowska et al., 2021). Additionally, substances contained in snail mucus, such as agglutinin, acharan sulfate, achacin protein and glycoconjugate are antimicrobial against *Escherichia coli*, *Streptococcus hemolysis*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Candida albicans* (Harti et al., 2016; McDermott et al., 2021; Pitt et al., 2015), and also inhibit the growth of *Staphylococcus epidermidis* (Santana et al., 2012). Nevertheless, certain reports have indicated that the antibacterial efficacy is significantly influenced by the snail species, the technique employed for collecting snail mucus, and the resistance exhibited by the organism under examination (El Zawawy et al., 2020; EL-Zawawy and Mona, 2021). Additional research has to be conducted to explore the antibacterial properties of snail mucus, particularly in relation to snail species other than *Achatina fulica*.

The reduction in the number of PMN leukocytes induced by snail mucus was associated to the secretion of bioactive compounds that participate in PMN leukocyte chemotaxis towards bacteria present at the wound site, so that a faster inflammatory response is likely the result of the antimicrobial activity of snail mucus. Additionally, VEGF and PDGH, which stimulate angiogenesis, also accelerate the inflammatory and wound healing processes (Rosanto et al., 2022; Santana et al., 2012). Administration of snail mucus can reduce the expression of MPO in wound and can reduce the presence of mast cells within 14 days after administration of snail mucus every day. Neutrophils and mast cells are two types of immune cells that play a crucial role in the inflammatory process. Mast cells serve as a significant source of diverse biologically active released substances. According to a study carried out by Gugliandolo, et al. (2021), a comparison to the control group resulted in a very high expression level of the pro-inflammatory cytokines IL-1β and TNF-α, whereas in wound treated with snail mucus for 14 days showed a decrease in the expression level of IL-1β and TNF-α, were also able to restore TGF-β levels in the wound bed.

Acharan sulfate and glycoconjugate in snail mucus play a role in the proliferative phase (Damayanti et al., 2020; Shoviantari et al., 2021). The proliferative phase is characterized by the presence of granulation tissue which is rich in new vascular tissue, fibroblasts, macrophages, granulocytes, endothelial cells and collagen which form the ECM and neovascular. In the proliferative phase there are three main processes, namely angiogenesis, fibroblasts, and re-epithelialization. In the process of angiogenesis, several growth factors, which are produced by endothelial cells, macrophages, fibroblasts, and keratinocytes, are involved in angiogenesis, for example VEGF, basic fibroblast growth factor (bFGF), fibroblast growth factor (FGF), TGF-β and lymphotoxin-alpha (LT-α). Macrophages will also produce pro-angiogenic factors such as VEGF, fibroblast growth factor-2 (FGF-2), angiopoietin-1 (ANGPT1), and thrombospondin (Bryant and Nix, 2016; Miloro et al., 2011; Primadina et al., 2019). Administration of snail mucus can increase the number of new blood vessels that are formed, this is due to the influence of GAGs, heparan sulfate, heparin sulfate, and hyaluronic acid contained in snail mucus which can increase angiogenesis by triggering VEGF (Jeong et al., 2001; Vieira et al., 2004). In the results of a study conducted by Rosanto et al. (2021), administration of snail mucus with concentrations of 48% and 96% had a significant effect on angiogenesis by forming new blood vessels in the lumen consisting of endothelial cells and containing erythrocytes due to the effect of the content of GAGs and heparan sulfate. The findings of this study are supported by research conducted by Ricci et al. (2023) that administration of snail mucus can induce the development of new blood vessels, as indicated by the expression of the ANGPT1 gene, which functions as a protective growth factor in both physiological and pathological angiogenesis promoting vascular phenotypes, sufficiently increased when snail mucus is administered after triggering an inflammatory stimulus. Meanwhile, angiopoietin-2 (ANGPT2) appeared to be reduced after administration of snail mucus, thus further supporting the positive modulation of pro-angiogenic signaling.

Heparan sulfate in snail mucus is also effective in increasing the production of fibroblast cells in this phase of wound healing (Riyani et al., 2021; Suarni and Badri, 2016). In the testing the number of fibroblast cells, the average number in the control group was 34.4 cells and the average in the wound group that was administrated snail mucus was 70.2 cells (Oroh et al., 2015). The number of fibroblast cells can be considered as a parameter of wound healing. During the proliferative phase, there will be an increase in cells number and the presence of wound healing factors, including the proliferation of fibroblasts. Fibroblasts are responsible for the secretion of collagen, which seals the wound and influences the re-epithelialization process. Fibroblasts have an important role, which is to produce ECM that fills the wound cavity and provides a base for keratinocyte migration. Macrophages produce PDGF, FGF, and TGF-β which induce fibroblasts to proliferate, migrate, and form ECM. Fibroblasts use matrix metalloproteinases-12 (MMP-12) to breakdown the fibrin matrix and replace it with GAGs. The ECM is then replaced by type III collagen produced by fibroblasts which will be replaced by type I collagen in the remodeling phase (Primadina et al., 2019). In this case, acharan sulfate and heparan sulfate, one of the proteoglycans, have the most effect on fibroblast proliferation because they function as binders and reservoirs of bFGF which is secreted into the ECM, will also interact with pro-angiogenic factors, such as FGF, VEGF, and PDGF (Oroh et al., 2015).

The aim of the remodeling phase is to optimize the strength and structural integrity of the newly formed tissue, while facilitating epithelial proliferation and the development of scar tissue. During this phase, contraction of the wound and collagen remodeling occur. This occurs due to the activity of fibroblasts which differentiate under the influence of TGF-β to become myofibroblasts, which will express α-SMA which will make the wound contract (Bryant and Nix, 2016; Velnar et al., 2009). Snail mucus has effectiveness in the remodeling process as shown by the results of a comparative test on the effectiveness of snail mucus and the control group in the form of surgical sutures and two medical adhesives containing cyanoacrylate (CA) and fibrin, conducted by Deng et al. (2023), and the study results stated that after the application of snail mucus, adhesion to the wet wound tissue occurred significantly compared to the control group. After 7 days of treatment, snail mucus showed better adhesion than CA and fibrin. These findings are corroborated by the research conducted by Gugliandolo et al. (2021), wherein it was observed that histological analysis wound tissue samples on day 14 indicated that the control group showed incomplete coverage of the wound bed by the epidermis. In contrast, the group treated with snail mucus showed enhanced wound closure, granulation, and re-epithelialization, collectively contributing to a near-complete restoration of the epidermis. Thus, it can be concluded that snail mucus is effective in enhancing the wound healing process in the remodeling phase. Additionally, through immunohistochemical analysis to assess the expression of α-SMA and VEGF, which are appropriate markers of the wound healing process, because VEGF is the main regulator of angiogenesis and α-SMA is a marker of cell differentiation, on administration of snail mucus, the expression of α-SMA and VEGF increased significantly on day 14, indicating proper wound healing and regulation of skin structure (Gugliandolo et al., 2021).

Administration of snail mucus significantly increased collagen content by measuring the presence of the COL3A1 gene which increased after 14 days of healing. The regulation of collagen deposition and maturation is modulated by several factors, including the matrix metalloproteinase (MMP) family. In the testing, snail mucus can prevent wound-induced overexpression of MMP-1, MMP-2, and MMP-9 factors (Gugliandolo et al., 2021), because overexpression of MMP impairs the remodeling and re-epithelialization phases (Mulholland et al., 2005). Usman and Salikunna (2015) added that by administrating snail mucus to the wound, the wound would heal faster. This was proven in the results of their study comparing the healing of wound treated with and without snail mucus, with an average wound healing time of 6.75 days and 8.1 days, respectively. So, it can be concluded from some of the scientific evidence reviewed above that snail mucus has activity in the process of wound healing, has effectiveness in enhancing wound healing, and has better wound healing results than wound that is not treated with snail mucus.

5. Conclusion

Based on the evidence presented in the discussion, we concluded that administration of snail mucus has an effect on wound healing, including post-tooth extraction wound, by enhancing the processes of hemostasis, inflammation, proliferation, and remodeling.

Limitation and Suggestion

The limitation of this literature review is the lack of high-quality research. Furthermore, the lack of information on the specific doses of snail mucus used and the duration of treatment are critical difficulties that should be addressed in future research to allow for more comprehensive meta-analysis. Additionally, it is required to conduct testing and comparative analysis of the composition of snail mucus across other species in order to ascertain the efficacy of snail mucus content in species other than *Achatina fulica*.

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