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Review Article

Utilisation of Snails for Wound Healing: A Review

Diana Fadhilah[1], Putra Santoso[1], Rita Maliza[1]*
1)Department of Biology, Faculty of Mathematics and Natural Sciences, Andalas University, Limau Manis, Padang 25163, West Sumatra, Indonesia
* Corresponding author, email: ritamaliza@sci.unand.ac.id

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ABSTRACT
Snails exhibit remarkable adaptability, allowing them to flourish in diverse environmental conditions and resulting in thriving populations in specific regions. This abundance has led communities to harness snails for various purposes, including their use as animal feed, daily dietary source, and in traditional wound-healing practices with historical roots. The primary objective of this systematic review is to identify the snail species commonly employed in wound healing and evaluate the bioactivity of compounds derived from different snail species. This review was conducted using literature review method, drawing from international databases such as Scopus, and encompassed publications from 2013 to 2023. A total of 22 articles met the inclusion and exclusion criteria. Snail body parts that have been explored for wound-healing purposes include both the body and the shell, along with snail secretions, particularly their mucus. Various methods have been employed to extract mucus, involving manual stimulation of the snail's body, spraying with a saline solution (NaCl), application of electric shock, and the use of ozone gas through nebulisation. Prominent snail species found to be beneficial for wound healing include *Achatina fulica*, *Helix aspersa*, *Eobania desertorum*, *Helix lucurus*, *Cornu bistrialis*, *Theba pisana*, and *Megalobulimus lopesi*. These snail species demonstrate potential applications in the treatment of burns, excision wounds, incision wounds, and diabetic ulcers. Key compounds within snail secretions encompass mucopolysaccharides, polyphenols, peptides, and glycosaminoglycans. These compounds exert significant effects on haemostasis, inflammation control, cellular proliferation, and re-epithelialisation, significantly contributing to the wound healing process.

INTRODUCTION

Molluscs are an abundant group of animals that serve a vital part in the animal kingdom’s trophic hierarchy. All of snail’s part are useful especially its mucus, shell, and body without shell. Snail’s mucus is a mucous fluid that shield the whole surface of the animal and secreted by particular salivary epidermal glands on the snails feet (Greistorfer et al. 2017). It was used by snails for various purposes, including movement, self-defense, identifying prey, and mating (Newar & Ghatak 2015).

Molluscs contain several thousands of bioactive chemicals. It includes peptides, terpenes, sterols, polypropionates, nitrogen compounds, fatty acid derivatives, macrolides, and alkaloids (Ulagesan et al. 2018). Snail mucus mostly consists of large polymers that are rich in carbohydrates and some small proteins that can relieve stomach pain because the mucus can neutralise stomach acidity and gastroesophageal reflux (Benkendorff et al. 2015). Furthermore, snail flesh contains high levels of protein, vitamins, and omega-3-fatty acids. It has a healthy balance of essential amino acids, including lysine, isoleucine, leucine, and phenylalanine (Kehinde et al. 2020).

Snails have been used for generations to treat a wide range of medical situations (Benkendorff et al. 2015). The mucus obtained from snails is applied to the skin to manage dermatitis, inflammation, acne, calluses, and to speed up wound alleviating (Ulagesan et al. 2018). Additionally, it can be used in respiratory problems and stomach pain (El-Zawawy & Mona 2021). Several bioactive chemicals have been studied, especially for their cytotoxic, antimicrobial, antitumor, antileukemic, antineoplastic, and antiviral properties in this gastropods group (Ulagesan et al. 2018; El-Zawawy & Mona 2021).

Wound healing is a complicated process that restores impaired cells and tissue to normal. It is a biological response to injury that involves the activation of fibroblasts, macrophages, and endothelial cells. Apart from that, a proper integration of the biological and molecular mechanisms of cell migration as well as proliferation is also required (Ulagesan et al. 2018). The recovery process is divided into four phases: haemostatis, inflammation, proliferation, and remodeling. These phases serve as a framework for considering the fundamental concepts of wound healing. Through these considerations, medical professions can improve their ability to care for injured bodies and assist in healing complex tissues. Wounds that never heal encourage health workers to look for the main cause that has not been resolved (Pawar & Shamkuwar 2023). Healing chronic wounds requires patient-centered, comprehensive, evidence-based therapy, interdisciplinary, and cost-effective (Pawar & Shamkuwar 2023).

Because the large population of snails and their compound content have health potential, as well as the high number of injuries that occur in the world, a literature review about the use of snails for wound healing is required. Therefore, this literature review can be used as a source of information to find out the potential of snails for the health sector, especially healing various wounds.

METHODS

This article was written using the literature review method (Figure 1). This method required international indexed article sources obtained from the Scopus website. The keywords used in searching for article sources were wound and slime. There were inclusion and exclusion criteria for selecting articles based on the year the article was published, type of article, language, open access, and type of source. After that, selection was carried out based on related topics through screening of article titles and abstracts.

The inclusion criteria of this article were articles on the topic of wound healing, using primary data and publication year <10 years, 2013-2023. The articles used were original articles and full text indexed by Scopus Q1-Q4, as well as were open access. The selected articles must be in English.

The exclusion criteria for this article were topics on tumor cell line, tumor invasion, cancer prognosis, carcinogenesis, cancer growth, tumor growth, cancer staging, tumor xenograft, liver cell carcinoma, breast cancer, lung tumor, cancer cell, cancer survival, tumor marker, stomach cancer, cancer tissue, and colorectal cancer. Articles in the form of review journals, short reposts, and case reports are also not used in this article.

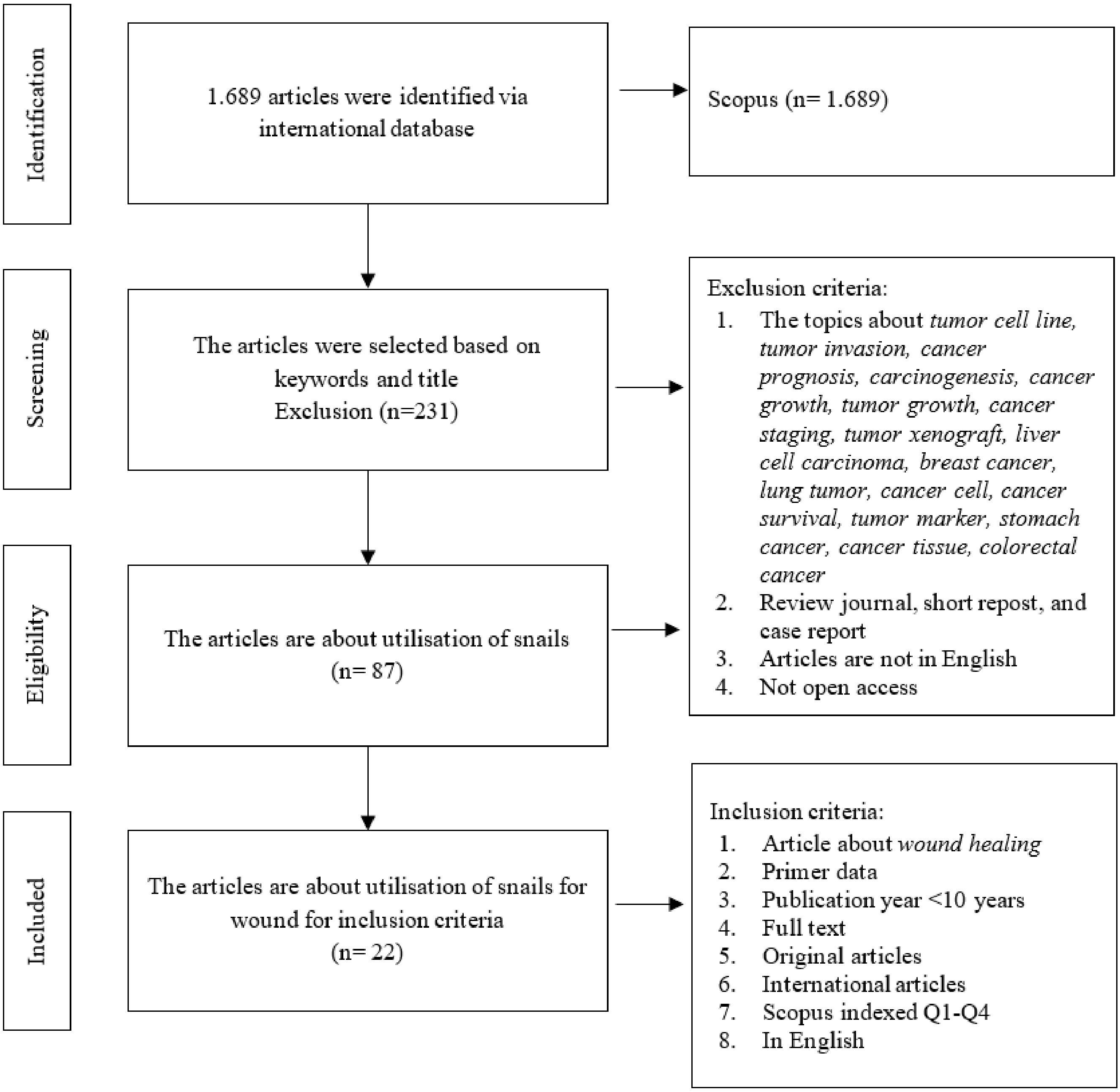

Figure 1. PRISMA diagram of article selection in systematic reviews.

In addition, this article did not use articles that are not in English and are not open access.

RESULTS AND DISCUSSION

In the identification stage, there were 1,689 articles found through international databases. The international database used in the article search is Scopus. In the screening stage, articles found in the identification stage were then selected based on keywords “wound” and “snail”, as well as article titles, so that 231 articles were excluded from related topics. After that, at the eligibility stage, articles related to snail utilisation were reviewed. Then, at the included stage, articles related to the use of snails in wound healing with inclusion criteria were selected.

Snail mucus collection

Snail mucus can be obtained by various methods. The amount of mucus obtained differs depending on the species and method used. Once the mucus is collected, it can be stored in different ways as shown in Table 1.

Table 1. Snail's mucus collection methods.

No.	Species	Amount	How to collect mucus	How to store	Reference
1.	*Helix aspersa*	15 snails produced 100 mL of mucus	Manually stimulating the pedal glands in the legs	Sterilized with a 0.45µm membrane and stored at -80°C, lyophilized to store in a dry state	El-Zawawy & Mona 2021
		500 snails (about 10 kg) produced 600 mL of mucus	The snails were sprayed with 3% NaCl and waited for 45 minutes	After sterilized with a peristaltic pump and 0.2 µm filter, the samples were kept at 4°C or -80°C.	Gentili et al. 2020; Mencucci et al. 2021
2.	*Helix aspersa muller*	-	Stimulated manually with the tip of a sterile cotton swab	Sterilized with filters measuring 10 µm, 1 µm, and 0.22 µm, then stored at 4°C	Gugliandolo et al. 2021a
		-	Using ozone gas in a few hours	Directly used in the next process as soon as possible	Gubitosa et al. 2020
3.	*Eremina desertorum*	15 snails produced 100 mL of mucus	Manually stimulating the pedal glands in the legs	Sterilized with a 0.45µm membrane and stored at -80°C	El-Zawawy & Mona 2021
4.	*Achatina achatina*	-	The snail is euthanized with an electrical shock of 5 – 10 volts for 30 – 60 s	Lyophilised then stored at temperature 4°C	Nworah et al. 2022
5.	*Eobania vermiculuta*	-	Stimulated manually by a sterile needle	Lyophylised and stored at -20°C	El-Attar et al. 2022
6.	*Achatina fullica*	-	Touching and pressing the snail's body by a sterile glass stick	Centrifuged at 10×g for 5 minutes, stored at 4°C	Agustina et al. 2020
		-	Stimulated by an electric shock 5 - 10 volt for 30 – 60 s	Macerated 24 h at 40° C, processing through precipitation	Harti et al. 2018
		50 snails produced 550 – 600 mL of mucus	Stimulated by an electric shock 1.5 volt for 30 – 60 s	Stored in the freezer	Putri et al. 2020
		A snail produced 3 – 5 mL mucus	Swiped by the tip of a syringe	Directly used in the next process as soon as possible	Igaap et al. 2023

Snail mucus can be obtained by stimulating the snail pedal using the tip of a tool such as a sterile cotton swab and sterile needle (Gugliandolo et al. 2021a; El-Attar et al. 2022). The mucus that has been obtained is sterilised to maintain the pH of the mucus using various filter sizes in micrometers. This is also done to remove impurities and endotoxins that can hinder the injection of mucus for chemical characterisation (Gugliandolo et al. 2021a).

Apart from physical stimulation, to get mucus, snails can be sprayed with 3% NaCl. Giving low concentrations of NaCl can cause stress in the snails so that mucus can be produced, and the mucus is collected in sterile tubes. Mucus collection was carried out for 45 minutes. After that, the snails are given water and returned to their habitat. The process that takes place in this method does not cause death to the snails (Gentili et al. 2020). Electric shock with varying electrical intensities and durations, 1.5 – 10 volts for 30 – 60 seconds, can also be used to collect snail mucus (Putri et al. 2020; Nworah et al. 2022). Although this procedure was simple and effective, the snails that were employed will die.

For an advanced method, snail mucus can be obtained by natural gases such as ozone. The mechanical extraction entailed the application of technology, which allowed us to obtain the mucus in a matter of hours. Specifically, the snails were put in a device that nebulized ozone for roughly an hour; the O_3 creates a kind of intensity that drives mucus production while minimising stress for the snails (Gubitosa et al. 2020).

The storage of snail's mucus can be achieved by either keeping fresh mucus at low temperatures or by lyophilizing it before processing and long-term storage. Longer lasting storage of mucus can be done by drying it via the lyophilisation method overnight. From this process a solid powder will be obtained which can be used for biological characterisation (El-Zawwy & Mona 2021). Fresh mucus is typically preserved in a freezer at temperatures ranging from -80°C to -20°C or in a refrigerator at 4°C.

Identification of snails for wound healing

This review has identified snail species with promising medicinal potential for wound healing. The utilised parts for wound healing include the body, shell, and mucus. Within the snail's body parts, a range of compounds with roles in wound healing have been discovered, and their biological effects are documented, as presented in Table 2.

Healing of excision wounds in mice can occur more quickly by Snail Secretion Filtrate (SSF) from *H. aspersa muller's* SSF can significantly increase the speed and percentage of wound closure. Based on histology, the re-epithelialisation process assisted by SSF was also better than that which was not given SSF. This is related to an increase in the amount of collagen in the wound area treated with SSF. Collagen is a part of the extracellular matrix which has a major involvement in wound healing at each phase (Fleck & Simman 2010). Apart from that, SSF also helps in the creation, deposition, and maturation of new collagen. This event is modulated by metalloproteinases (MMPs) which are key to wound matrix modification (Gugliandolo et al. 2021a).

Diabetes mellitus patients have a sluggish recovery of the wound process. Diabetes mellitus is a metabolic illness identified by chronic hyperglycemia that leads to a variety of consequences, including foot ulcers and poor wound healing. Despite receiving sufficient and prompt care, diabetic patients' wounds could remain for weeks. Fibroblast proliferation in the later stages of wound healing is associated with the recovery of structure and function at the wound site (Ulagesan et al. 2018). Diabetes impairs macrophage responses and the phenotypic transition from M1 to M2 (Deng et al. 2023).

The use of Cb-peptide ointment on diabetes-induced excisional wounds can accelerate wound contraction and re-epithelialisation. Diabetes-induced cuts also showed an increase in tensile strength when treated with Cb-peptide ointment compared to the control group due to a rise in collagen concentration and fiber stabilisation. This shows that collagen has an important function in wound healing (Ulagesan et al. 2018). Additionally, mucus *A. fulica* demonstrated a healing effect on diabetic wounds, which assists in encouraging the transformation of wound recovery from the inflammatory to the proliferative stage (Deng et al. 2023).

The active material composition of snail mucus contributed to its wound healing potential (Figure 2). Chemicals found in snail's mucus included achatin isolates and heparan sulfate. The achatin isolates were antibacterial and analgesic, and calcium aids in haemostasis. Snail mucus' antibacterial and antiinflammatory characteristics accelerated the inflammatory and proliferative stages of wound healing (Harti et al. 2018).

Table 2. Types of snails whose mucus is used in wound healing

No.	Species	Part of body	Utilisation	Compound	Effect	Reference
1.	*Achatina fulica*	Mucus	Burns, cuts	Protein, glycosaminoglycans, acharan sulfate, allantoin, metallic element	Increasing the number of basal epithelial cells	Putri et al. 2020; Song et al. 2021; Nworah et al. 2022; Deng et al. 2023
2.	*Helix aspersa*	Mucus	Excision wound	Thiophene, 3-(decyloxy) tetrahydro-1,1-dioxide, 4-(nonafluoro-tert-butyl) nitrobenzene, glycosaminoglycans, glycolic acid, allantoin, polyphenols, sugar, collagen, mucopolysaccharides	Antimicrobial, increases cell migration and speed of tissue repair, anti-inflammatory	Gentili et al. 2020; Gugliandolo et al. 2021a; El-Zawawy & Mona 2021
3.	*Helix aspersa muller*	Mucus	Wound repair, potential for skin damage caused by pollution, gastric ulcers	Glycolic acid, allantoin, polyphenols, mucopolysaccharide, hyaluronic acid, collagen, elastin, vitamin A, vitamin B, vitamin E, copper, nickel, chromium	Cell proliferation and migration, antimicrobials, skin protection, protects against O_3 exposure by preventing oxidative damage and pro-inflammatory responses, regulation of inflammation	Trapella et al. 2018; Gentili et al. 2020; Gugliandolo et al. 2021b
4.	*Eremina desertorum*	Mucus	Wound	7-bromoheptyl ethyl ester, methyl 1,2-benzisothiazole-3 -acetate, 3H-1,2,4-triazole-3-thione, 4,5-dihydro-4,5-diphenyl,	Antimicrobial, anti-inflammatory, cell proliferation and migration are regulated by TGF-β1 and VEGF gene expression	El-Zawawy & Mona 2021
5.	*Helix lucorum*	Mucus	Wound	Protein, glycosaminoglycans, allantoin, metallic element	Decreasing the blood loss in haemostasis	Deng et al. 2023
6.	*Cryptozona bistrialis*	Mucus peptides	Excision and incision wounds	Peptides	Antimicrobial, fibroblast proliferation, collagen synthesis	Ulagesan et al. 2018
7.	*Tibia curta*	The body of a snail without a shell	Excision wound	Fatty acids, sterols, alkanes, amino acids	Reduction of skin thickness	Ragi et al. 2016; Pawar & Shamkuwar 2023
		Shell	Excision wound	-	Reduction of skin thickness	Pawar & Shamkuwar 2023
8.	*Megalobulimus lopesi*	Shell	Diabetic ulcer	Calcium carbonate	Accelerates wound closure, stimulates angiogenesis, increases calcium concentration in the wound area, controls the expression of cytokines and growth factors	Andrade et al. 2018

Heparan sulfate, a component of snail mucus that affects fibroblast proliferation, was beneficial in accelerating wound healing by aiding in blood coagulation and fibroblast cell proliferation. Heparan sulfate also enhances angiogenesis by reducing vascular endothelial growth factor (VEGF) and decreasing the mitogenic activity of fibroblast growth factor (FGF) (Vieira et al. 2004; Harti et al. 2018).

Chitosan in *A. fulica* had the best results in vitro for lymphocyte proliferation activity, outperforming 100% snail's mucus and 5% snail mucus cream. Leukocytes and their differentiation provide body defenses for mice. White blood cells, or leukocytes, are some of the most active blood cells in the body's defense mechanism (Joe et al. 2004; González-Lamothe et al. 2009). White blood cells identify and eliminate infections during immunological reactions, as well as aiding in inflammation and healing (Rajakaruna et al. 2002; Fadillah & Santoso 2019). Snail's mucus and 5% chitosan can be used to create galenic anti-inflammatory lotions. In vitro, snail mucus creams and chitosan galenic formulations were helpful for lymphocyte proliferation and wound healing. (Harti et al. 2018).

Chronic wounds are treated with antibiotics, anti-inflammatory treatments, or a combination of the two, but some of these medications have a number of side effects. As a result, safer alternatives are required. Several investigations have been conducted to develop optimal clinical wound healing biomaterials (Ulagesan et al. 2018). In addition to the concentration of active substances such as snail's mucus, using ointments or gels as part of the preparation might prevent adverse effects by lowering the total dose required to achieve the aim (Goyal et al. 2016; Whittam et al. 2016; Refiani et al. 2021).

Mucus composition changes depending on species and mechanical factors such as temperature, light intensity, humidity, food supply, and soil conditions. The physical features of snails, like as colour and mucus viscosity, are also influenced by environmental factors. *H. aspera* snail mucus is colourless and thinner than *E. desertorum* (desert snail) mucus, which is somewhat hazy white and viscous. Desert snails' high viscosity mucus works as a barrier, reducing moisture loss and protecting them from bacterial diseases (El-Zawawy & Mona 2021).

H. aspersa muller's mucus extract promotes mammalian fibroblast survival, proliferation, and migration. Fibroblasts are the predominant cell type in granulation wound tissue. Fibroblasts play a vital role in wound healing by secreting growth factors that promote proliferation, angiogenesis, and matrix deposition (Ulagesan et al. 2018). The biological effects of snail's mucus on cell proliferation and migration may have consequences for wound healing and therapeutic drug development (Trapella et al. 2018). *H. aspersa muller*'s mucus contains mucopolysaccharide, polyphenols, hyaluronic acid, and other bioactive compounds, as well as minerals (Gugliandolo et al. 2021a).

The key compounds found in snails contributing to wound healing include the following:

a. Mucopolysaccharide

   H. aspersa muller's mucus contains mucopolysaccharide, which enhances mucus adhesion to the skin, and polyphenols, which have the potential to prevent oxidative damage. Moreover, this species' mucus can stimulate endogenous hyaluronate synthesis, boosting the skin's water binding capacity and viscoelasticity (Trapella et al. 2018; Gentili et al. 2020). Increasing mucus adhesion to the skin, which serves as a barrier, can protect epithelial cells from pollution (Gentili et al. 2020).

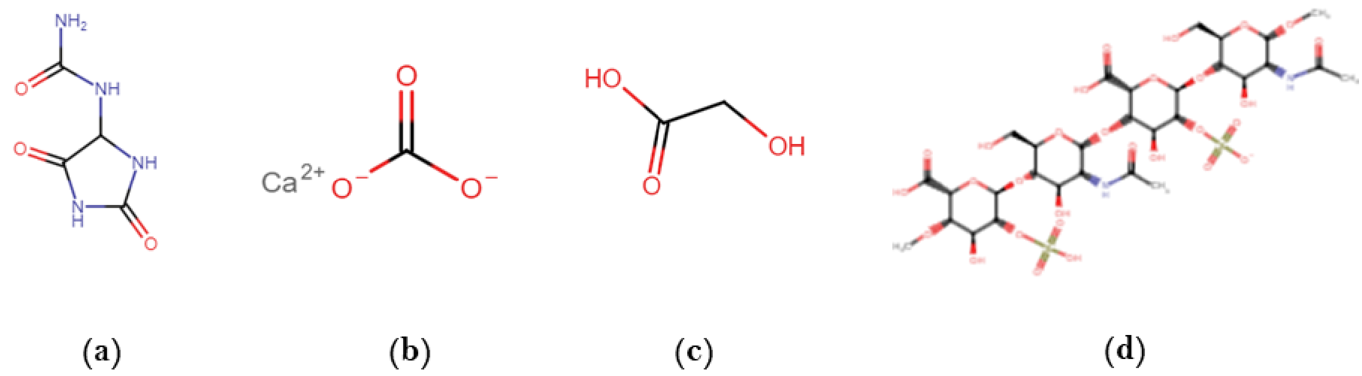

Figure 2. Chemical structure of compounds in snails that have functions in wound healing; allantoin (a), calcium carbonate (b), glycolic acid (c), acharan sulfate (d).

b. Polyphenols

Polyphenols in *H. aspersa*'s mucus can activate defense mechanisms such as the NRF2 pathway, triggering an antioxidant response capable of correcting tissue redox imbalances caused by O_3. Through the activation of NRF2, a mixture of natural compounds such as vitamin C, vitamin E, and ferulic acid can reduce ozone-induced oxidative stress in keratinocytes, RHE, and human skin, indicating that the harmful effects of ozone can be modulated by tissue antioxidant responses. Polyphenols can also help to prevent and treat pollution-induced cutaneous oxidative damage (Gentili et al. 2020).

c. Peptides

One of the finest examples is the use of tiny compounds that are both inexpensive and functional in increasing the production of endogenous wound healing agents such as peptides. Peptides are biomaterials that have many bioactivities related to wound healing (Ulagesan et al. 2018).

Peptide of *Cryptozona bistrialis* (Cb-peptide) significantly increased the response to migration in the scratch wound test. In addition, Cb -peptide also shown considerable cellular activity in diabetes-induced excisional wounds (using Alloxan), including maximum collagen deposition, blood vessel regeneration, and significant epithelialisation (Ulagesan et al. 2018).

d. Glycosaminoglycan

In general snail's mucous contains glycosaminoglycan with acharan sulfate sulfate. It has the repeated disaccharide units of →4)-2-acetamido-2-deoxy-α-D glucopyranose (1→4) -2-sulfo-α-L-idopyranosyluronic acid (1→(GicNAc-IdoA2SO3-) (Joo et al. 2005; Putri et al. 2020). Glycosaminoglycan molecules are composed of carbohydrates, uric acid, dissolved globular proteins, and oligoelements (calcium, copper, iron, and zinc). Glycosaminoglycans of snails (*A. fulica*) are related to the heparin sulfate family and serve to accelerate wound recovery by increasing blood coagulation and fibroblast cell proliferation (Vieira et al. 2004; Agustina et al. 2020).

Microbial infection is the main factor influencing the wound healing process (Ulagesan et al. 2018). To prevent infection from microbials, much research has been done on antimicrobial peptides because they have a wide biochemical diversity and specialisation regarding antiviral, antibacterial, antifungal, antiprotozoal, and antitumor or wound healing effects (Ulagesan et al. 2018). The antibacterial activity is also possessed by several types of snails as shown in Table 3.

Table 3. The antimicrobial activity of various snail's mucus extracts

No.	Species	Types of microbes	Reference
1.	*H. aspersa*	*Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Aspergillus niger, Rhizopus stolonifer, Trichoderma harzianum, Candida albicans*	El-Zawawy & Mona 2021
2.	*E. desertorum*	*P. aeruginosa, E. coli, S. aureus, A. niger, R. stolonifer, T. harzianum, C. albicans*	El-Zawawy & Mona 2021
3.	*C. bistrialis*	*S. aureus, P. aeruginosa, C. albicans, M. racemosus*	Ulagesan et al. 2018
4.	*Pomacea canaliculata*	*S. aureus, Methicilin-Resistant Staphylococcus aureus (MRSA), S. epidermidis, Corynebacterium sp.*	Nantarat et al. 2019
5.	*Lissachatina fulica*	*S. aureus, MRSA, S. epidermidis, Corynebacterium sp*	Nantarat et al. 2019
6.	*A. fulica*	*C. albicans, Penicillium chrysogenum, Aspergillus fumigatus, Hafnia alvei, Serratia mercescens, S. aureus*	Ulagesan & Kim 2018
7.	*C. bistrialis*	*C, albicans, P. chrysogenum, A. fumigatus, Mucor racemosus, P. aeruginosa, P. vulgaris, H. alvei, S. mercescens, S. aureus, Micrococcus luteus*	Ulagesan & Kim 2018
8.	*Pila globosa*	*A. fumigatus, M. racemosus, S. aureus*	Ulagesan & Kim 2018
9.	*Pila virens*	*C. albicans, A. fumigatus, P. chrysogenum, M. racemosus*	Ulagesan & Kim 2018
10.	*Bellamya dissimilis*	*M. racemosus*	Ulagesan & Kim 2018
11.	*Bithynia pulchella*	*P. chrysogenum*	Ulagesan & Kim 2018

Snail mucus' antibacterial activity is determined by the snail species, the extraction procedure, and the organism's resistance. *E. desertorum*'s mucus has strong inhibitory efficacy against certain resistant bacteria, including *E. coli*, *P. aeruginosa*, *S. aureus*, *A. niger*, *R. stolonifer*, *C. albicans*, and *T. harzianum*. *E. desertorum* mucus is more effective than *H. aspersa* mucus against resistant bacteria associated with burn wound infections (El-Zawawy & Mona 2021). Those microorganisms were found in various wounds, even acute and chronic wounds. Pathogens such as bacteria, fungi, and viruses can impair wound healing by a variety of processes, the most common of which are infection and inflammation at the wound site. In addition, they are related to delayed healing and complications (Bowler et al. 2001).

CONCLUSION

Based on the result of reviewing 22 articles, it was defined about snail's mucus collection methods, as well as types of snails, its components, and its biological activities. Snail mucus can be collected by stimulating the snail's body with friction, NaCl spray, electric shock, and nebulized ozone gas. Types of snails used in wound healing, namely *A. fulica*, *H. aspersa*, *E. desertorum*, *H. lucurus*, *C. bistrialis*, *T. curta*, and *M. lopesi*. The body parts of snails that can be utilized in wound healing are the whole body, mucus, and shell. The dominant component in snails are mucopolysaccharides, polyphenols, peptides, and glycosaminoglycans. The snails can be used for some wound type such as burns, excision wounds, incision wounds, and diabetic ulcers.

AUTHOR CONTRIBUTION

The study's conceptualisation was done by DF, PS, and RM, while DF carried out data analysis and manuscript preparation. The manuscript's content was reviewed and approved for publication by all the authors.

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CONFLICT OF INTEREST

There is no conflict of interest in this article.

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