



The Effectiveness of Galenic Cream of Seromuroid of Snail and Chitosan for Chronic Wound Treatment

Agnes Sri Harti¹(✉), Rahajeng Putriningrum², Joko Santoso³, Sutiyo Dani Saputro¹, Saelan Saelan¹, and Yusup Subagio Sutanto⁴

¹ Departement of Nursing, Kusuma Husada University of Surakarta, Surakarta 57127, Indonesia
agnessriharti168@gmail.com

² Midwife Professional Study Program, Faculty of Health Sciences, Kusuma Husada University Surakarta, Surakarta 57127, Indonesia

³ Department of Pharmacy, Faculty of Health Sciences, Kusuma Husada University of Surakarta, Surakarta 57127, Indonesia

⁴ Pulmonary Disease Study Program, Faculty of Medicine, Sebelas Maret University of Surakarta, Surakarta 57126, Indonesia

Abstract. Background: A wound is a form of tissue damage to the skin caused by physical, chemical, and physiological conditions. Treatment of chronic wounds takes a relatively long time so a wound care process or wound management using traditional or modern medical therapy is needed. The development of material-based galenic formulations containing bioactive compounds which can be used for wound care management.

Aim: This research was to test and analyze the effectiveness galenic cream preparations of snail seromuroid and chitosan for wound care in vitro.

Methods: The method was based on the experimental design with the research stages covering bioformulation of galenic cream preparations of snail seromuroid and chitosan as well as testing the quality of galenic preparations physically, chemically, and microbiologically. Analysis of observational data was statistically tested using the One Way Anova.

Results: Bioformulation of seromuroid galenic cream 2.5% and chitosan 2.5% and their combination ratio (1:1), (1:2); (2:1) according to the requirements of BPOM No. 32 of 2019, it eligible the requirements for the quality test of cream preparations in a physicochemical manner including pH, antioxidant activity, dispersion, and adhesion and microbiologically includes Total Plate Number, Yeast Mold Number, and no microbial pathogens *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*.

Conclusion: Preparation of seromuroid cream and chitosan and their combination ratio (1:1), (1:2); (2:1) can be formulated into galenic cream preparations that can be applied for the treatment of chronic wounds.

Keywords: Snail Seromuroid · Chitosan · Galenic · Cream · Chronic Wound

1 Introduction

Chronic wounds are wounds that fail to heal in the expected time, the recovery process is slow, more than 12 weeks, and sometimes can cause disability. The duration of chronic wound treatment is relatively long, so a wound care process or wound management using traditional or modern medical therapy is needed. The treatment of chronic wounds is still dominated by the use of synthetic chemicals or patented drugs. Synthetic drugs are considered to have many weaknesses, namely relatively expensive prices, side effects if the product not been registered, has not considered wound healing properties, and only acts as an antiseptic or inducing angiogenesis, so it is relatively ineffective for the treatment of chronic wounds [1]. In general, what is considered in the selection of wound cream products is price, convenience, and product safety.

The current issue of wound care is often associated with generative diseases and metabolic disorders in patients, so proper wound care management is needed so that the wound healing process can be optimal. This is due to the addition of new innovative products for wound care. One of the wound treatments is to treat the wound using topical preparations. Topical preparations are drug preparations that are used at the site of the lesion [2]. The provision of appropriate and effective topical preparations is expected to reduce and prevent infection in wounds. The topical dosage form was chosen because it has several advantages, namely, it is comfortable to use and easily absorbed into the skin, gives a cool and non-sticky feeling, avoids difficulties in drug absorption with food, avoids risks, and is able to stop the effects of drugs quickly if clinical action is needed [3].

The follow-up to Harti et al.'s research results from the PDUPT program to facilitate DRPM for the 2019 and 2020 fiscal years and the Simple Patent No. S00202010479 showed a synergistic effect of bioactive compounds seromuroid snails and chitosan as biological response modifiers or bioimmunostimulators and antimicrobial agents so that they can be developed as anti-inflammatory galenic preparations. The purpose of the study was to analyze the effectiveness of galenic preparations of snail seromuroid and chitosan in vitro for the treatment of chronic wounds.

2 Methods

This type of research is based on experimental research and was conducted at the Pharmacy Laboratory of Kusuma Husada University Surakarta, the Pharmacology Laboratory of Setia Budi University Surakarta, and partner An Nafii Home Care Surakarta. The time of implementation is from March to July 2022. The research stages include handling and preparation of snail seromuroid, 2% chitosan, cream formulation and quality test.

The description of ethical approval of this research with letter number No.: 789/VI/HREC/2020 has been approved by the Health Research Ethics Committee Dr. Moewardi General Hospital.

The tools used are a centrifuge, spectrophotometer, autoclave, incubator, membrane filter, oven, pH meter, electric shock, millipore filter, tissue culture plastic, diagnostic reagents (ELISA, cholesterol, Biuret, Bradford), electric scales (Mettler Toledo), tools sterile surgical instruments (Smicss), Eppendorf tube, centrifuge (Sorvall.), micropipette

(Brand), sterile Petri dish (Costar), 10 mL injection syringe (Terumo), centrifugation tube (Nunc), vortex (Bio-Rad), microscope (Olympus).

Materials used are local snails (*Achatina fulica*), Biotechsindo medical grade chitosan, culture media (PCA, SGA, BHI, VJA, MSA), chemical reagents (Tris HCl, sodium acetate buffer, physiological NaCl, aqua dest), Gram dye, microbial isolate (*Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*).

2.1 Isolation of Snail Seromuroid

Samples of local snails (*Achantina fulica*) as many 10–50 snails, were taken by opening the end of shell and the liquid was accommodated in the flask. and centrifuged at 3000 rpm for 30 min as hemolymph fluid or can be carried out by electric shock from an electric current of 5–10 V, for 30 -60 s. The mucus was macerated on water for 24 h at 4 °C. The water-soluble fraction of slime is known as WSF (Water soluble fraction) then was obtained by adding an absolute ethanol ratio of 1:3. WSF and mixture were centrifuged at 2900 g for 30 min. The precipitation was redissolved with Tris-Cl and obtained the mucin fraction [4].

2.2 Preparation of Chitosan 2%

The medical-grade chitosan used in the study was produced by PT Biotechsindo Cirebon Indonesia. The 2% chitosan concentration used was based on the results of previous studies [5].

2.3 Bioformulation of Galenic Preparations of Snail Seromuroid Cream and Chitosan

The formulation used as a galenic preparation of snail seromuroid cream and chitosan is a modification of the previous research formulation [6].

2.4 Quality Test of Galenic Preparations of Snail Seromuroid Cream and Chitosan

The quality test for galenic cream preparations of snail seromuroid and chitosan, refers to the safety and quality requirements of traditional medicines from the Food and Drug Monitoring Agency of the Republic of Indonesia number 32 of 2019. The quality test of the preparation includes an organoleptic test, a physicochemical test, and a microbiological test.

2.5 Data Analysis

Analysis of the observational data was tested statistically using the One Way Anova test, which had previously been tested for homogeneity and normality prerequisites. The normality test uses the Shapiro-Wilk test because the number of samples is less than 50. If the significance is > 0.05 then it is normally distributed and then the paired T-test is carried out. If the significance is < 0.05 then it is not normally distributed, then the Wilcoxon test is performed.

Table 1. Organoleptic test of seromuroid of snail and chitosan cream

Code	Formulation	Consistency	Cream type	Texture	Color	Odor
F0	Basis cream	Cream	O/W	Homogenous	Pure white	Normal, no smell
F2	Chitosan (C) 2%	Cream	O/W	Homogenous	Pure white	Normal, slightly sour
F6	Snail seromuroid (SS) 2.5%	Cream	O/W	Homogenous	White bone	Normal, no smell
F12	C:SS = 1:1	Cream	O/W	Homogenous	White bone	Normal, no smell
F13	C:SS = 1:2	Cream	O/W	Homogenous	White bone	Normal, no smell
F14	C:SS = 2:1	Cream	O/W	Homogenous	White bone	Normal, no smell

3 Results

The formulation used as a galenic preparation of snail seromuroid cream and chitosan is a modification of the previous research formulation [6]. The formulation of snail seromuroid cream and chitosan from 5 formulas based on differences in the composition of snail seromuroid, chitosan, and their combination.

3.1 Organoleptic Test

An organoleptic is an assessment of product quality based on the five human senses assessing the quality of food, pharmaceutical, or other product including taste, smell, color, and texture [7]. The organoleptic test for the preparation of galenic cream of snail seromuroid, chitosan, and their mixture was carried out visually covering the components of consistency, texture, color and odor. The organoleptic test for the cream preparations of snail seromuroid snail and chitosan included consistency, type of cream, texture, color, and aroma as listed in Table 1.

3.2 Cream-Type Test

Based on the cream-type test, the preparation of snail seromuroid cream and chitosan has an O/W type as shown in Fig. 1. The cream-type test is conducted of 1 g of cream smeared on a glass slide and dripped with methylene blue until it spreads over the cream, then observed with a microscope. The methylene blue dye will dissolve in the water phase, so the water phase will be blue (blue globules). If it is seen even blue color so the cream is an oil-in-water or O/A type.

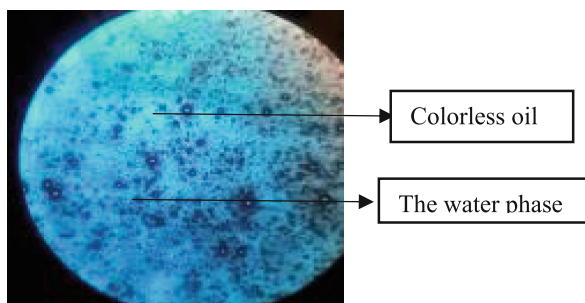


Fig. 1. The results of the cream-type test

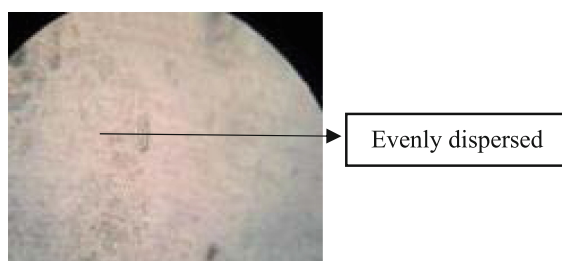


Fig. 2. Homogeneity test results

3.3 Homogeneity Test

The aim of homogeneity is to see uniformity. Homogeneity examination on all cream preparations showed homogeneous results, marked by all particles being evenly dispersed on the slide and no clumping in each preparation, which can be seen in Fig. 2.

3.4 Heavy Metal Contamination Test

The heavy metal contamination test was carried out at Surakarta Goods Quality Certification Testing Agency due to limited equipment at the institution on 19 July–16 August 2022. The heavy metal contamination test is actually not included in the quality test preparation for wound care creams, but considering its application as a cream on the skin as cosmetics, a heavy metal contamination test was carried out with the results listed in Table 2.

3.5 Test the Quality and Stability of Galenic Cream Preparations

Test the quality and stability of galenic cream preparations from snail seromuroid, chitosan, and their mixtures based on pH, spreadability, and adhesion. The adhesion test to determine the ability of the cream preparation that adhere to the applied on the skin. Determination of dispersion is carried out with an extensometer, which is where the sample is placed with a certain volume in the center between two glass plates, where the

Table 2. Heavy metal test preparation of snail seromuroid galenic cream and chitosan

Code	Formulation	Level mg/kg					Quality Requirements SNI 01-2896-1998	Conclusion
		Pb	Cd	Hg	As	Sn		
F0	Basis cream	49.769	<0.0053	<9.6 x 10 ⁻⁵	<5.1 x 10 ⁻⁴	Negative	<ul style="list-style-type: none"> • Pb max 20 mg/kg • Cd max 5 mg/kg • Hg max 1 mg/kg • As max 5 mg/kg • Sn negatif 	Qualify
F2	Chitosan (C) 2%	40.176	<0.0053	<9.6 x 10 ⁻⁵	<5.1 x 10 ⁻⁴	Negative		Qualify
F6	Snail seromuroid (SS) 2.5%	41.412	<0.0053	<9.6 x 10 ⁻⁵	<5.1 x 10 ⁻⁴	Negative		Qualify
F12	C:SS = 1:1	42.178	<0.0053	<9.6 x 10 ⁻⁵	<5.1 x 10 ⁻⁴	Negative		Qualify
F13	C:SS = 1:2	38.491	<0.0053	<9.6 x 10 ⁻⁵	<5.1 x 10 ⁻⁴	Negative		Qualify
F14	C:SS = 2:1	40.881	<0.0053	<9.6 x 10 ⁻⁵	<5.1 x 10 ⁻⁴	Negative		Qualify

upper plate is loaded with weights placed on it [8]. Measurement of the pH which using a digital pH meter that has been calibrated using a standard buffer solution [2].

The quality and stability test of cream preparations is based on changes in the measurement value of pH, adhesion, and dispersibility during the storage period, namely day 0 and day 20 when stored at cold temperatures with the assumption that the change in measurement value will be lower at the beginning of the measurement and the next measurement period. To determine the significance of changes in the stability of the preparation, the resulting data were analyzed statistically as listed in Table 3.

The bivariate analysis on the stability of the preparation with One-Way Anova based on pH that a p-value of 0.799 > 0.05, so for the 5 formulations there was no significant difference in the stability of the preparation to changes in pH. Meanwhile, based on the dispersion power without load, 50 g load, 100 g load, and 250 g load showed that p-value > 0.05, there was no significant difference in dispersion of the preparation. The stability of the preparation is based on the adhesion test that p-value < 0.05, so there is a significant difference in the adhesion of the preparation.

3.6 Microbial Contamination Test

Microbial contamination testing is carried out with reference to the requirements of the Food and Drug Monitoring Agency of the Republic of Indonesia number 32 of 2019 to

Table 3. The quality and stability of galenic cream preparations

Variable	Mean		P-value	Description
	Pre	Pos		
pH	6.8900	6.8563	0.799	p-value > 0.05 there is no difference
Spreadability				
No load	3.3225	3.4700	0.362	p-value > 0.05 there is no difference
Load 50 g	3.7513	3.8425	0.055	p-value > 0.05 there is no difference
Load 100 g	4.0525	4.0113	0.062	p-value > 0.05 there is no difference
Load 250 g	4.5000	4.0113	0.052	p-value > 0.05 there is no difference
Adhesion	24.6112	10.1813	0.012	p-value < 0.05 there is a difference

Table 4. Microbial contamination test preparation of snail seromucoid galenic cream and chitosan

Code	Formulation	Microbial Contamination Test					Requirements Food and Drug Monitoring Agency of the Republic of Indonesia number 32 of 2019.	Conclusion
		Total Plate Number (TPN)	Yeast Mold Number (YMN)	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>		
F0	Basis cream	0	0	Negative	Negative	Negative	<ul style="list-style-type: none"> • TPN ≤ 2 x 10² CFU/g • YMN ≤ 2 x 10 CFU/g • <i>S. aureus</i>: negatif/g • <i>P. aeruginosa</i>: negatif/g • <i>C. albicans</i>: negatif/g 	Qualify
F2	Chitosan (C) 2%	0	0	Negative	Negative	Negative		Qualify
F6	Snail seromucoid (SS) 2.5%	0	0	Negative	Negative	Negative		Qualify
F12	C:SS = 1:1	0	0	Negative	Negative	Negative		Qualify
F13	C:SS = 1:2	0	0	Negative	Negative	Negative		Qualify
F14	C:SS = 2:1	0	0	Negative	Negative	Negative		Qualify

determine the quality and safety of galenic [9] including Total Plate Number, Yeast Mold Number, absence of pathogenic microbes are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans* as listed in Table 4.

4 Discussion

The composition galenic cream of snail seromucoid and chitosan can affect the quality test of cream preparations. The use of stearic acid in cream has a concentration requirement of 1–20% (10). Stearic acid with triethanolamine (TEA) forms a creamy base when mixed with 5–15 times of the aqueous solution. The appearance of stearic acid has white or yellow colored crystals, crystalline solid, or white, the solubility of stearic acid is easily soluble in benzene, carbon tetrachloride, chloroform, ether, soluble in ethanol, hexane, and propylene glycol, practically insoluble in water [3]. Stearic acid is a commonly used cream base along with TEA as an emulsifier and alkalizing agent to produce

a homogeneous and O/W stable emulsion when combined with free fatty acids. Creams using steric acid and TEA showed stability during storage. Nipazol and nipagin in the formula function as preservatives to prevent damage to cream preparations [11].

The results of the organoleptic test of the 5 formulations met the requirements for cream preparations that could be applied to the skin, namely homogeneous cream form, normal aroma, and relatively white to brownish color which was influenced by the seromuroid color of the snail. The slightly sour smell is influenced by the solvent chitosan is an acidic solution, but the slightly sour smell is still under normal conditions that do not cause irritation to the skin.

The cream preparation is defined as a semi-solid preparation or thick emulsion with a water content of less than 60% and is used for external use [12]. Creams that meet the organoleptic requirements are having a color like the active substance, a characteristic aroma of the extract, and an appearance like a creamy mass. An organoleptic test is an assessment of product quality based on the five human senses. Many researchers use the five senses to assess the quality of a product, especially agricultural and food products. The criteria commonly used to assess a product include taste, smell, color, and texture [13].

Cream preparations from snail seromuroid and chitosan belong to the type of o/w cream or oil in water, this is based on the methylene blue color which is soluble in water and looks evenly distributed. The presence of stearic acid in the o/w type cream can make the cream softer, that the viscosity becomes low so that the release of the drug from the base will be small [3].

The homogeneity test on the preparation of snail seromuroid cream, chitosan, and their mixtures showed uniformity of particles in the cream preparation so as to provide good and maximum quality when used. Homogeneity is one of the factors that can affect the physical quality of cream preparations. The homogeneity test was carried out to visually determine the distribution power of the active substance of the cream. The cream is declared homogeneous if there is an overall uniform color match and there are no particles in the cream [14].

The results of the examination of heavy metal contamination showed that the preparation of galenic cream of seromuroid snails and chitosan did not contain heavy metal contamination, referring to the quality requirements of cream preparations according to SNI 01-2896-1998 and BPOM Regulation Number 12 of 2019 concerning contamination in cosmetics so that it is safe when applied as cream preparations. for skin wounds.

In measurement pH of the galenic cream preparations of snail seromuroid and chitosan, it is still safe because it is still below neutral pH so it does not cause irritation when applied to the skin. The pH range of cream preparations that are acceptable to the skin ranges from 4.0 to 7.5 [15]. The degree of acidity of the cream preparation is influenced by the content of the extract compounds and the ingredients of the formula. pH is an important part of every preparation that aims to measure the level of acidity or alkalinity of preparation [16]. A pH value that is too acidic can cause itchy and scaly skin, and a pH value exceeding 7 is feared to cause skin irritation [17].

The adhesion test was carried out to determine the adhesive ability of the cream preparations related to the application of the cream to the skin. This is done because the cream will relate to the duration of contact of the cream with the skin to get the

therapeutic effect achieved. A good value for the adhesion of the cream is 2–300 s [11]. Based on the value of the adhesion range of 2.00–300.00 s, the preparations of galenic cream of seromucoid snail and chitosan meet the specified requirements.

Spreadability test is the ability of a preparation to spread in the place where the preparation is applied and is one of the characteristics responsible for the effectiveness of the preparation. The cream is said to be easy to apply and evenly distribute and the surface area of the skin in contact with the cream because it is in the range of requirements of 5–7 cm [8]. Testing the spreadability of cream is an important requirement for cream preparations. The active substance will be spread and it will be more effective in producing its therapeutic effect. The results of testing the spreadability of galenic cream preparations did not meet the specified dispersion range. This is influenced by the composition of the cream preparation. Low values can be affected by high viscosity. Preparations that do not meet the spreadability requirements will reduce the comfort and effectiveness of the preparation when used on the skin. Changes in the ability to spread the cream will have an impact on the cream being difficult to spread on the skin when applied which will affect the effectiveness of the cream on the skin and make the user uncomfortable because of its very thick consistency.

Stability testing of the preparation was carried out during the storage process at low temperatures for a period of 20 days. The significant difference for each variable was influenced by the type and composition of the ingredients for galenic cream preparations. The stability of preparation is characterized by the ability of a drug or cosmetic product to survive within the specified limits. Stable cosmetic preparations are characterized by preparations that do not change during the period of storage and use, where their properties and characteristics do not change the same as when they were originally made [18].

The results of microbial contamination showed that the galenic cream of snail seromucoid cream and chitosan as well as the combination met the requirements of the Food and Drug Monitoring Agency of the Republic of Indonesia number 32 of 2019 microbiologically as galenic preparations including Total Plate Number, Yeast Mold Number, absence of pathogenic microbes *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*. Microbiological quality is very important because the presence of microbes in cosmetic preparations can not only damage the preparation but the most important thing is that some of the microbes are pathogenic so they can cause infection. The safety and quality of cosmetics depend on raw materials, packaging materials, facilities, equipment, production processes, quality control, and labor involved in production.

The effectiveness of chitosan as an antimicrobial is influenced by the degree of deacetylation of chitin linked to the 1,4 b-glucosamine bond, while the activity of chitosan as an antimicrobial is related to the Chito-oligosaccharida compound which is polycationic so as to suppress the growth rate of pathogenic microbial Gram-negative and Gram-positive bacteria, including *Escherichia coli*, *Staphylococcus aureus*.

The various types of achasin proteins in snail seromucoids are glycoproteins; α -1 globulin-ormucoid fraction; glycans, peptides, and chondroitin sulfate, have very important biological functions, namely as bacterial enzyme binding receptors so that

they can function as immunomodulators and immune suppressants [19, 20]. The bactericidal and/or bacteriostatic effectiveness of snail mucus against *Staphylococcus sp*, *Streptococcus sp*, and *Pseudomonas sp* isolates showed varying results [21].

Snail seromucous at a concentration of 100% was able to be bacterial against *Staphylococcus aureus*, *Candida albicans*, and *Pseudomonas aeruginosa*. 100% snail seromucous and 5% snail seromucous cream preparation have an effective effect in accelerating the healing time of second degree burns (A). The immunostimulatory effects of seromuroid snails and chitosan can be used to increase the body's immunity against infection with facultative intracellular pathogenic bacteria [22].

The results of the study showed that the combination of 100% snail mucus and 1.5% chitosan = 1:2 showed an optimum level of wound healing in vivo and a synergistic effect between chitosan and snail seromucosa against the bacteria that causes ulcers, namely *Staphylococcus aureus* in vitro.

5 Conclusions

Preparation galenic cream of snail seromuroid and chitosan and their combination ratio (1:1), (1:2); (2:1) can be formulated into galenic cream preparations and meet the quality test based on the requirements of the Food and Drug Monitoring Agency of the Republic of Indonesia number 32 of 2019 so that it is effective and safe to be applied as a galenic cream preparation for the treatment of chronic wounds.

Acknowledgments. This study was supported by P2VUPT program research scheme in 2022 (128/SPK/D4/PPK.01. APTV/VI/2022 and 006/LL6/AK.04/ PPKM.PTV/2022) of the Ministry of Education and Culture, Research, Technology, Directorate General of Vocational Education.

Authors' Contributions. A.S.H. responsible for developing ideas and organizing for research, microbiological test. Y.S.S. as supervisor of literature and critical review. J.S. and R.P. responsible for bioformulation and quality testing of galenic cream preparations. S.D.S. responsible for methodological design, collected analyzed of data. S.S. responsible for collecting clinical specimens, and assaying wound healing rates in vivo. All author were responsible the manuscript and contribution to the final article.

Declaration of Competing Interest. The authors declare no conflict of interest.

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