

## DEVELOPMENT OF SUNSCREEN PRODUCTS CONTAINING *Stichopus hermanii* Semper, 1868

Ulfi Widyowati<sup>1</sup>, Erza Genatrika<sup>1</sup>, Asmiyenti Djaliasrin Djalil<sup>1\*</sup>

Department of Pharmacy, Faculty of Pharmacy, Universitas Muhammadiyah Purwokerto,  
Purwokerto, 53182, Indonesia

\*Email Corresponding: [asmiyentidjaliasrindjalil@ump.ac.id](mailto:asmiyentidjaliasrindjalil@ump.ac.id)

Submitted: December 24, 2023    Revised: August 15, 2024    Accepted: August 27, 2024

### ABSTRACT

Prolonged radiation from UV sunlight has been known to be responsible for skin damage. Sunscreen has been used to limit sun exposure. Sunscreen with natural ingredients has the potential to be developed along with the issue of side effects of synthetic ingredients. This study aimed to develop a zoocuticals sunscreen cream containing a *Stichopus hermanii* Semper, 1868 extracts. The sunscreen creams were formulated with various ingredients of extract include 0.05 (F1), 0.1 (F2), and 0.2 (F3) %, respectively. The in vitro sun protection factor, organoleptic properties, homogeneity, pH, viscosity, spreadability, and adhesion of the creams were evaluated. F3 met the requirements of physical properties. The extract show sun-protective efficacy with SPF value of 2.11 (F1), 3.09 (F2), and 3.46 (F3). Sunscreen containing 0.2% of *Stichopus hermanni* extract is the most preferred formulation with minimal protection category.

**Keywords:** Sea Cucumber, *Stichopus hermanii* Semper, 1868, Sunscreen.

### INTRODUCTION

Moderate sun exposure can cause skin damage (Polefka *et al.*, 2012). The sun's rays range from the ultraviolet (UV) to the infrared spectrum. The UV radiation from the UVA (320–400 nm) to the UVB (290–320 nm) is unsafe for human skin. Sunscreen is a common way to avoid the harmful effects of sun exposure. Sunscreens support the body's natural defenses to prevent sunburn from UV rays and provide protection against skin cancer. Sunscreens come in many forms, including gels, sticks, sprays, lip balms, lotions, and creams. Creams and lotions were most commonly used.

Today, alternative or complementary cosmetics using natural ingredients are becoming popular. It has also been reported that natural sunscreens are more appropriate for hyperallergic skin (Kapoor *et al.*, 2009). Some herbs, such as coconut, olive, castor, almond, peppermint, chaulmoogra, mustard, sesame, lemongrass, lavender, eucalyptus, and orange provide essential protection from harmful UV rays (Kaur & Saraf, 2010). In addition, animal-derived cosmetic components called zoocuticals were also gaining popularity. Animal-based materials might be utilized as functional substances, extra components, or fundamental ingredients. The materials such as snail mucus, lanolin, and marine collagen were often polyfunctional. Sea cucumbers (*Stichopus hermaini* Semper, 1868) have the potential to be further developed as cosmetic ingredients (Cristiano & Guagni, 2022).

Sea cucumber has long been used to produce traditional medicines such as gamat oil and gamat water (Zohdi *et al.*, 2011). These species are popular among consumers, medical professionals, and biomedical researchers because of their potential health benefits. The sea animal contains secondary metabolite compounds, including steroids, sapogenins, saponins, triterpenoids, glycosaminoglycans, lectins, alkaloids, phenols, and flavonoids (Bordbar *et al.*, 2011; Rasyid, 2012). Other ingredients of sea cucumber, such as amino acid components,

collagen, and vitamin E, can slow cell degeneration, which means declaration of the aging process (Senadheera *et al.*, 2020).

Many natural sources from plants or animals have features that allow them to absorb UV light, such as conjugated double bonds, aromatics, and auxochrome groups. Additionally, certain compounds in natural sources have been found to have antioxidant properties. Previous research indicates that *Stichopus hermaini* has the potential to be an antioxidant with an IC<sub>50</sub> value of 65.08 ppm, while the sea cucumber *Holothuria leucospilota*, *H. Lessi*, *Stichopus broadus*, *S. quadrifasciatus*, and *B. marmorata* show IC<sub>50</sub> values of 155.07, 163.83, 209.45, 245.85, and 382.86 µg/mL, respectively (Rasyid, 2012; Rasyid *et al.*, 2023). These combination properties provide more protection against the harmful effects of UV light exposure.

Sunscreens are now incorporated into moisturizers, creams, lotions, and other skin preparations. In a previous study, topical skincare creams were developed with sea cucumber *Holothuria arenicola* extract as antioxidants (Ayman *et al.*, 2020). Another study prepared powder of sea cucumber (*Holothuria scabra*) as an antioxidant (Ansharullah *et al.*, 2022). Until now, no research has focused on formulating *S. hermaini* as a sunscreen. Hence, this study aimed to formulate a cold cream preparation from *Stichopus hermaini* Semper, 1868, as a sunscreen.

## RESEARCH METHODS

### Materials

Sea cucumber (dried) was cultivated in Kalipuro, Banyuwangi, Indonesia. Methanol (technical grade), cera alba, liquid paraffin, span 80, methyl paraben, propyl paraben, fragrance oleum rosae (pharmaceutical grade), and distilled water were purchased from Brataco Chemical (Indonesia).

### Research Procedure

#### 1. Preparation of Sea Cucumber Powder

Sea Cucumber was collected from Banyuwangi. The animal was authenticated in the Laboratory of Zoology Taxonomy, Faculty of Biology, Jenderal Soedirman University, Purwokerto, Indonesia.

#### 2. Extraction of Active Compounds from Sea Cucumber Powder

Sea cucumbers (without the entrails) were dried, ground into a powder, and then sieved using a no. 20/60 sieve until a fine powder was produced. Moreover, sea cucumber powder maceration was carried out using methanol solvent.

#### 3. Sunscreen Formulation

The basic sunscreen formulation was prepared as outlined in the EIRI recommended formulation with some modifications (EIRI Board of Consultants and Engineers, 2007). Several cream formulations containing 0.05 (F1), 0.1 (F2), and 0.2% (F3) sea cucumber extract were designed (Table I). The cold cream was prepared by mixing liquid paraffin, cera alba, propylparaben, and span 80. The compounds were heated at 70°C and poured into a warm porcelain mortar. Afterward, methylparaben, distilled water, and sea cucumber extract were poured into the mixture. When it gets cold, the cream is added with oleum rosae (Murniati & Sari, 2014; Rahayu *et al.*, 2023).

#### 4. Organoleptic and Physicochemical Evaluation

These sunscreens were subjected to organoleptic evaluation, including texture, color, and odor. Observations were carried out every week for 30 days. The physicochemical evaluation of the cold cream was confirmed for viscosity, homogeneity, spreadability, organoleptic, adhesion, and pH. Viscosity was measured using an LV-4 spindle (Brookfield viscometer). The rotation was set to 60 RPM. The homogeneity test was evaluated as follow: Cream 0.1 g was applied on a piece of glass. The homogeneous cream should show a uniform composition and no visible spots. Another test, spreadability, was performed by measuring the spreading diameter of 0.5 g cream between two circular glass plates (diameter 15 cm) after one minute. The upper plate's

standard weight was 50 g. The increase in diameter due to cream spreading was observed. Finally, the adhesion test was determined by measuring the detachment time between two plates. Cream 1 g was placed between two glass plates. A load (1 kg) was applied to the top plate for 5 min. Next, the load was removed, the plate was given a load release of 80 g.

##### 5. Preliminary Stability Test

The cream was stored at temperatures of 27°C (ambient temperature) for one month and evaluated for viscosity and pH.

##### 6. SPF Measurement

The efficacy of sunscreen cream (SPF) was measured using a UV-visible spectrophotometer (Shimadzu type AY220). The samples were prepared using the protocol described by Mansur *et al.* (1986) (Dutra *et al.*, 2004; Mansur *et al.*, 1986). One gram of sample was weighed and diluted to 100 mL with ethanol. After 5 minutes of sonication, the solution was filtered, and the first 10 mL was discarded. Aliquots were diluted 50 times with ethanol. The absorbance of each prepared aliquot was then measured at 5 nm intervals in the range of 290–320 nm using ethanol as a blank. The SPF was calculated using the Mansur equation as follows:

$$SPF = CF \times \sum_{290}^{320} EE(\lambda) \times I(\lambda) \times Abs(\lambda)$$

where CF=correction factor (10), EE (λ)=erythmogenic effect of radiation at wavelength λ, Abs (λ)=spectrophotometric absorption value at wavelength λ.

**Table I. Content of the Formulations**

Ingredients	Concentration of Formula (% w/v)			
	F1	F2	F3	Base
Sea cucumber extract	0.05	0.1	0.2	0
Cera alba	16	16	16	16
Liquid paraffin	45	45	45	45
Span 80	5	5	5	5
Methylparaben P	0.1	0.1	0.1	0.1
Propylparaben	0.02	0.02	0.02	0.02
Oleum rosae	0.1	0.1	0.1	q.s
Distilled water	q.s. up to 100	q.s. up to 100	q.s. up to 100	100

## RESULTS AND DISCUSSION

The proposed formula composition obtained a cream with organoleptic characteristics, as seen in Table II. The physicochemical characteristics of this cream meet the cream requirements according to SNI 16-43399-1996 (Badan Standardisasi Nasional, 2016). Sea cucumber before and after drying and in powder form can be seen in Figure 1.



**Figure 1. (A-C). Fresh (A), dried (B), and powder (C) of *Stichopus hermaini* Semper, 1868.**



**Figure 2.** Cream preparation with various *Stichopus herrmanni* Semper, 1868 extracts.

The cream made was a type of W/O (water-in-oil) cream, often called cold cream. This type of cream has a better spread. Although slightly oily, the evaporation of water can reduce the feeling of heat in the skin (Sirsat *et al.*, 2022). The water phase and oil phase were mixed with the emulsifier span 80. The aqueous phase contains distilled water, while the oil phase contains liquid paraffin and cera alba, which serve as cream bases. Furthermore, oleum rosae was fragrant, while methyl and propylparaben were preservatives. *Stichopus hermanii* methanol extracts sunscreen cold cream have a soft, semi-solid, and white texture (Figure 2).

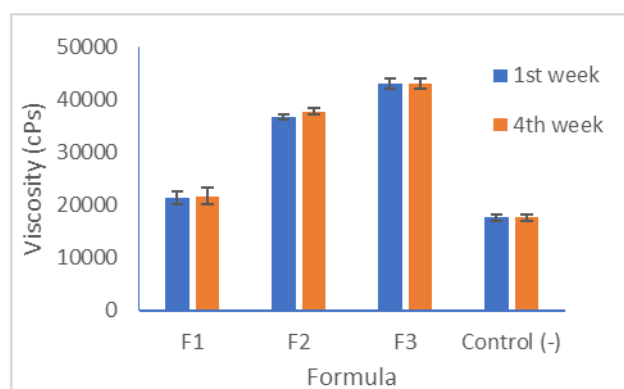
Several physicochemical tests were conducted on the formulated sunscreen cream, and the results are shown in Table II. *Viscosity*. The viscosity of the formulated sunscreen creams ranged from 21333 to 43000 cPs. Since cream is a non-Newtonian system with a solid heterogeneous dispersion, the viscosity was tested using a Brookfield viscometer (Kornaeva *et al.*, 2023; Martin *et al.*, 1993). The SNI calls for a viscosity standard of 2,000 to 50,000 cPs for creams, while other recommendations indicate good viscosity values of 30,000 to 700,000 cPs (Badan Standardisasi Nasional, 2016; Buhse *et al.*, 2005). The result suggests that the cream has suitable viscosity. Viscosity is an important parameter for evaluating cream preparations, and its properties are related to the spreadability of the cream (Deuschle *et al.*, 2015). The viscosity values were compared between formulas (F1–F3 and base) and between storage intervals (one and four weeks) using a two-way ANOVA statistical analysis. In order to investigate further some parameters with distinct variable averages, post hoc Tukey tests were performed. The mean viscosity of cold creams was significantly higher than that of base ( $p$ -value < 0.05). The viscosity increases when the extract level becomes higher. Furthermore, the viscosity was monitored for 4 weeks to evaluate the stability of the cream. The results were shown in Figure 3. There was no difference in viscosity between fresh cream and cream after storage for 4 weeks ( $p$ -value>0.05).

**Table II.** Evaluation of the Sunscreen Cream Formulation Upon Fresh Preparation

Evaluation Parameters	Formula			
	F1	F2	F3	Base
Homogeneity	Homogen	Homogen	Homogen	Homogen
Texture	Semisolid	Semisolid	Semisolid	Semisolid
Colour	White	White	White	White
Odor	Characteristic of rose oil	Characteristic of rose oil	Characteristic of rose oil	Characteristic of rose oil
Viscosity (cps)	21333±1154	36666±577	43000±1000	17667±577
Spreadability (cm)	9.30±0.12	8.59±0.02	7.61±0.02	10.66±0.06
Adhesion (s)	4.14±0.09	4.53±0.04	4.87±0.33	3.15±0.02
pH	6	6	6	6
SPF	2.12±0.01	3.09±0.25	3.46±0.04	

a. Spreadability

The spreadability value is inversely proportional to the viscosity of a cream preparation. The spreadability will affect the speed of active compound diffusion through the membrane. The preparation of cream must be able to spread widely so that the diffusion of active substances occurs rapidly through the membrane and gives maximum effect (Deuschle *et al.*, 2015). The test results showed that the three formulas had a dispersion exceeding the sunscreen preparation standard recommended by SNI 16-43399-1996, which is 5–7 cm (Badan Standardisasi Nasional, 2016). However, formula 3 is the most affordable compared to other formulas (Table II), with a spreadability value of  $7.61 \pm 0.02$  (Kruskal-Wallis,  $p$ -value  $< 0.05$ ). Based on the data, the extract added affects the dispersion. The more extracts are added, the more the spreadability decreases. Therefore, the sea cucumber content can still increase beyond 0.2%, considering the viscosity within the required range.



**Figure 3.** Viscosity of cream containing *Stichopus hermaini* Semper extract after fresh preparation and storage for 1 month (two-way ANOVA, Tukey  $p < 0.001$ ;  $N = 3/\text{group}$ )

#### b. Adhesion

All prepared creams (F1–F3) have a good adhesion ( $> 4$  seconds). The concentration of the sea cucumber extract affects its adhesion. The increasing of the extract content, the more its adhesion ( $p$ -value  $< 0.05$ ). An adhesion test measures how well a cream sticks to the skin to produce the intended therapeutic effect. If the cream is too thick, it can block the skin, making it hard for it to breathe. However, if the adhesion is too weak, the cream won't have the desired therapeutic effect (Voight, 1995). Good adhesion for topical preparations is considered to be over 4 seconds (Pratasik *et al.*, 2019).

The results show that the three formulas have the pH recommended by SNI 16-4399-1996 (4.5–8) (Badan Standardisasi Nasional, 2016). The pH value refers to the pH value of the skin (4.5–7.5) (Yacobus *et al.*, 2019). The pH measurement aims to evaluate the safety of the cream preparation. Ideally, topical preparations have the same value as the skin's pH to avoid irritation on the skin's surface. Moreover, observations were made of changes in pH for one month. The results showed that during one month of storage, there was no change in the pH of all preparations. Changes in pH can indicate the stability of the active substance used.

#### c. SPF

Table II shows SPF values for F1, F2, and F3 as  $2.12 \pm 0.01$ ,  $3.09 \pm 0.25$ , and  $3.46 \pm 0.04$ , respectively. This value belongs to the category of minimal protection against UV B sunlight (290–320 nm). However, SPF cream can still be increased by increasing the extract concentration (one-way ANOVA, Tukey,  $p$ -value  $< 0.05$ ). Sea cucumbers contain compounds that can protect the skin from UV light. Flavonoids and saponin in sea cucumbers have properties that allow them to absorb UV light, such as conjugated double bonds, aromatics, and auxochrome groups. Additionally, flavonoids have antioxidant activity that helps protect the skin from UV light (Avigail *et al.*, 2019). Studies have also shown that saponin content in sea cucumbers can reduce free radicals and prevent degenerative diseases



caused by excess free radicals (Soltani *et al.*, 2014). *Stichopus hermaini* contains 47% protein, 0.8% fat, and 37.9% ash content, with the largest amino acid content being glycine and the largest fatty acid C20:1 n-9. High ash content indicates the potential of metal oxides that can provide physical protection (Wen *et al.*, 2010). Furthermore, A wide range of bioactive substances, particularly phenols, cerverosides, triterpene glycosides (saponins), sterols, chondroitin sulfates, and glycosaminoglycans (GAGs), contribute to the biological activities of sea cucumbers, including their role as a sunscreen (Bordbar *et al.*, 2011; Rasyid, 2012).

## CONCLUSION

*Stichopus hermaini* Semper methanol extract can be formulated as a sunscreen with minimal protection. Formulations with higher SPF and acceptable characteristics were demonstrated in cream containing 0.2% extract. The cream is stable for one month of storage at ambient temperature.

## CONFLICTS OF INTEREST

All authors have none to declare.

## REFERENCES

- Ansharullah, A., Patadjai, A. B., Asranudin, A., and Tamrin, T, 2022, Preparation of Sea Cucumber (*Holothuria scabra*) Powder: Effect of Pre-treatment on Its Nutritional, Antioxidant Activity and Morphological Characteristics, *Proceedings of the International Conference on Tropical Agrifood, Feed and Fuel (ICTAFF 2021)*. 17(Ictaff 2021) : 98–102. <https://doi.org/10.2991/absr.k.220102.016>
- Avigail, Y., Yudiati, E., and Pringgenies, D, 2019, Aktivitas Antioksidan dan Kandungan Total Fenolik Pada Teripang di Perairan Karimunjawa, Jepara, *Journal of Marine Research*. 8(4) : 346–354. <https://doi.org/10.14710/jmr.v8i4.24600>
- Ayman Saber Mohamed, Sohair Ramadan Fahmy, and Abdelaziz A. Elsayed, 2020, Formulation and Evaluation of the Sea Cucumber, *Holothuria arenicola* Extract Incorporated Skin Cream, *GSC Biological and Pharmaceutical Sciences*. 13(2) : 232–239. <https://doi.org/10.30574/gscbps.2020.13.2.0379>
- Badan Standardisasi Nasional. 2016. *SNI 16-4399-1996: Sediaan tabir surya*. Badan Standardisasi Nasional.
- Bordbar, S., Anwar, F., and Saari, N, 2011, High-Value Components and Bioactives from Sea Cucumbers for Functional Foods--A Review, *Marine Drugs*. 9(10) : 1761–1805. <https://doi.org/10.3390/md9101761>
- Buhse, L., Kolinski, R., Westenberger, B., Wokovich, A., Spencer, J., Chen, C. W., Turujman, S., Gautam-Basak, M., Kang, G. J., Kibbe, A., Heintzelman, B., and Wolfgang, E, 2005, Topical Drug Classification, *International Journal of Pharmaceutics*. 295(1–2) : 101–112. <https://doi.org/10.1016/j.ijpharm.2005.01.032>
- Cristiano, L. and Guagni, M, 2022, Zoochemicals and Cosmetic Ingredients Derived from Animals, In *Cosmetics*. (Vol. 9, Issue 1). <https://doi.org/10.3390/cosmetics9010013>
- Deuschle, V., Deuschle, R., Bortoluzzi, M., and Athayde, M, 2015, Physical Chemistry Evaluation of Stability, Spreadability, In Vitro Antioxidant, and Photo-Protective Capacities of Topical Formulations Containing *Calendula officinalis* L. Leaf Extract, *Brazilian Journal of Pharmaceutical Science*. 51 : 63–75. <https://doi.org/10.1590/S1984-82502015000100007>
- Dutra, E. A., Da Costa E Oliveira, D. A. G., Kedor-Hackmann, E. R. M., and Miritello Santoro, M. I. R, 2004, Determination of Sun Protection Factor (SPF) of Sunscreens by Ultraviolet Spectrophotometry, *Revista Brasileira de Ciencias Farmaceuticas/Brazilian Journal of Pharmaceutical Sciences*. 40(3) : 381–385. <https://doi.org/10.1590/S1516-93322004000300014>
- EIRI Board of Consultants and Engineers. 2007. *Cosmetics Processes and Formulations Hand Book with Herbal Cosmetics Technology and Formulae*. Engineers India

Research Institute.

- Kapoor, V. K., Dureja, J., and Chadha, R, 2009, Herbals in The Control of Ageing, *Drug Discovery Today*. 14(19–20) : 992–998. <https://doi.org/10.1016/j.drudis.2009.06.014>
- Kaur, C. D. and Saraf, S, 2010, In Vitro Sun Protection Factor Determination of Herbal Oils Used in Cosmetics, *Pharmacognosy Research*. 2(1) : 22–25. <https://doi.org/10.4103/0974-8490.60586>
- Kornaeva, E. P., Stebakov, I. N., Kornaev, A. V., Dremin, V. V., Popov, S. G., and Vinokurov, A. Y, 2023, A Method to Measure Non-Newtonian Fluids Viscosity Using Inertial Viscometer with A Computer Vision System, *International Journal of Mechanical Sciences*. 242 : 107967.
- Mansur, J. S., Breder, M. N. R., Mansur, M. C. A., and Azulay, R, 1986, Determinação do Fator de Proteção Solar por Espectrofotometria, *Anais Brasileiros de Dermatologia*. 61 : 121–124.
- Martin, A., James, S., and Arthur, C, 1993, *Farmasi Fisik: Dasar-Dasar Kimia Fisik dalam Ilmu Farmasetik*. UI-Press.
- Murniati, H. and Sari, D. I, 2014, Uji Pelepasan dan Aktivitas Glutation Sediaan Krim Tipe A/M menggunakan Cera Alba, *Jurnal Pharmascience*. 1(1) : 59–63.
- Polefka, T. G., Meyer, T. A., Agin, P. P., and Bianchini, R. J, 2012, Effects of Solar Radiation on The Skin, *Journal of Cosmetic Dermatology*. 11(2) : 134–143. <https://doi.org/10.1111/j.1473-2165.2012.00614.x>
- Pratasik, M. C. M., Yamlean, P. V. Y., and Wiyono, W. I, 2019, Formulasi dan Uji Stabilitas Fisik Sediaan Krim Ekstrak Etanol Daun Sesewanua (*Clerodendron squamatum* Vahl.), *Pharmacoon*. 8(2) : 261. <https://doi.org/10.35799/pha.8.2019.29289>
- Rahayu, P., Monica, E., and Yulinda Cesa, F, 2023, Formulasi dan Evaluasi Sediaan Krim Pelembab dan Antioksidan Kombinasi Ekstrak Kulit Buah Manggis *Garcinia mangostana* L dan Lidah Buaya *Aloe vera* L, *Sainsbertek Jurnal Ilmiah Sains & Teknologi*. 3(2) : 52–65. <https://doi.org/10.33479/sb.v3i2.234>
- Rasyid, A. 2012. Identification of Secondary Metabolites Compounds, Antibacterial, and Antioxidant Activities on The Methanol Extract of Sea Cucumber *Stichopus hermanni*. *Jurnal Ilmu dan Teknologi Kelautan Tropis*. 4(2): 360–368. <https://doi.org/10.28930/jitkt.v4i2.7799>
- Rasyid, A., Putra, M. Y., and Yasman, 2023, Antibacterial and Antioxidant Activity of Sea Cucum ber Extracts Collected from Lampung Waters, Indonesia, *Kuwait Journal of Science*. 50(4) : 615–621. <https://doi.org/https://doi.org/10.1016/j.kjs.2023.03.012>
- Senadheera, T. R. L., Dave, D., and Shahidi, F, 2020, Sea Cucumber Derived Type I Collagen: A Comprehensive Review, *Marine Drugs*. 18(9). <https://doi.org/10.3390/md18090471>
- Sirsat, S. V, Rathi, N. M., Hiwale, A. S., and Punam B Sheike, 2022, A Review on Preparation and Evaluation of Herbal Cold Cream, *World Journal of Pharmaceutical Research*. 11(5) : 690–697.
- Soltani, M., Parivar, K., Baharara, J., Kerachian, M. A., and Asili, J, 2014, Hemolytic and Cytotoxic Properties of Saponin Purified from *Holothuria leucospilota* Sea Cucumber, *Reports of Biochemistry & Molecular Biology*. 3(1) : 43–50. <http://www.ncbi.nlm.nih.gov/pubmed/26989736%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4757088>
- Voight, R. 1995. *Buku Pelajaran Teknologi Farmasi* (5<sup>th</sup> ed.). Universitas Gadjah Mada Press.
- Wen, J., Hu, C., and Fan, S, 2010, Chemical Composition and Nutritional Quality of Sea Cucumbers, *Journal of the Science of Food and Agriculture*. 90(14) : 2469–2474. <https://doi.org/10.1002/jsfa.4108>
- Yacobus, A. R., Lau, S. H. A., and Syawal, H, 2019, Formulasi dan Uji Stabilitas Krim Ekstrak Methanol Daun Beluntas (*Pluchea indica* L.) dari Kota Benteng Kabupaten Kepulauan Selayar Provinsi Sulawesi Selatan, *Jurnal Farmasi Sandi Karsa*. 5(1) : 19–25.

Zohdi, R. M., Zakaria, Z. A. B., Yusof, N., Mustapha, N. M., and Abdullah, M. N. H, 2011, Sea Cucumber (*Stichopus herrmanni*) based Hydrogel to Treat Burn Wounds in Rats, *Journal of Biomedical Materials Research. Part B, Applied Biomaterials*. 98(1) : 30–37. <https://doi.org/10.1002/jbm.b.31828>