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Optimisation of hand sanitiser gel formula of Tekelan leaves extract (*Chromolaena odorata*) using simplex lattice design method

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ABSTRACT

Background: Tekelan leaves (*Chromolaena odorata*) has been commonly used traditionally as a medicine. It is known that Tekelan leaves have bioactivity as an antibacterial. These leaves have antibacterial activity for both gram-positive and negative bacteria so that it can be made for semi-solid preparation namely hand sanitiser gel (HSG). This study aims to determine the optimum concentration of HSG base with TLE and determine the physical characteristics of the optimum formula.

Methods: Sample extraction was done by maceration method with 96% of ethanol (1:10). Dechlorophyllation with n-hexane also used to separate the chlorophyll and to get a better colour of extract while it formulated in gel form. Optimisation of the gel is conducted with the simplex lattice design (SLD) method. SLD method is available in Design-

Expert software. The method was designed to optimise the formula with different concentration of different component (Gliserin, TEA, and Carbopol) so it can produce the optimum formula. The evaluation of HSG involves spreadability test, sticky power and pH test. Furthermore, the acceptability evaluation was done by 20 respondents.

Results: The optimum gel base formula is consists of 1.860% glycerin, 2.901% TEA, and 0.739% carbopol with spreadability 3.673 cm, sticky power 1.181 s, and pH 7.187. The acceptability of the *C. odorata* HSG also compared with one of the commercial HSG. The percentage of acceptability of *C. odorata* HSG is 75.25% and 80.25% for the commercial HSG.

Conclusion: HSG preparations of TLE which are formulated using optimum base formula have good physical properties.

Keywords: Tekelan leaves (*Chromolaena odorata*), hand sanitiser gel, optimisation, Simplex Lattice Design, TLE, HSG

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INTRODUCTION

Diarrhoea is a disease with a high prevalence and mortality in developing countries such as Indonesia. *Riset Kesehatan Dasar* in 2016 showed that 130,561 cases of diarrhoea were found in West Nusa Tenggara, and also diarrhoea is the third largest cause of death after tuberculosis and pneumonia.^{1,2}

Diarrhoea is transmitted through faecal-oral, improper sanitation and hand hygiene will increase the probability of diarrhoea. Data from the World Health Organization (WHO) in 2009 showed that the total bacteria in the palm reached 39,000 - 46,000 CFUs/cm². These bacteria have a high potential to cause both gastrointestinal infections and other infectious diseases. The use of hand antiseptic has been proven to be able to contribute greatly to the prevention of diseases such as diarrhoea, acute respiratory infections (ARI) and avian influenza.^{3,4}

The use of hand sanitisers is increasingly popular in the community because it's practical application does not require any water source. Hand sanitiser products that sold in the community is used alcohol-based as active antimicrobial substances. However, the use of alcohol that is too often will

cause some side effects that are uncomfortable for consumers. Alcohol cause irritation reactions, burning sensation, dry skin, dermatitis, to respiratory problems and urticaria in response to alcohol hypersensitivity.¹

Seeing that alcohol-based hand sanitisers can have many adverse reactions to the consumers, so it is important to create hand sanitiser products that come from natural ingredients. The use of natural ingredients as sanitiser hand compositions tends to be safer, does not irritate, and respiratory problems. One of the natural ingredients that can be used as antimicrobials in hand sanitisers is Tekelan leaves (TL). Tekelan leaves (*Chromolaena odorata*) contain secondary metabolites such as phenolic, tannin, saponin, flavonoids, and steroids. Secondary metabolite compounds contained in Tekelan leaves show efficacy as an antimicrobial agent. At a minimum concentration of 0.25 mg/mL, the ethanol extract of the Tekelan leaves has been able to inhibit the growth of *Staphylococcus aureus* bacteria and at a minimum concentration of 0.125 mg/mL can inhibit the growth of *Escherichia coli* bacteria.⁴ Also, Yutika (2015) states that the strength of

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Tekelan leaves extract (TLE) to inhibit the growth of bacteria is classified as an intermediate activity. Scientific evidence for the antimicrobial activity of the Tekelan leaves makes it a candidate for bioactive substances in natural-based hand sanitiser. The use of TLE as the bioactive ingredients of hand sanitisers can reduce the harmful side effects caused by alcohol.⁵ Seeing the potential of Tekelan leaves as an antibacterial and the level of public interest in HSG, the purpose of this study is to determine the optimum concentration of Glycerin, TEA, and Carbopol as major components of HSG base and determine physical characteristics of the optimum formula of TLE.

MATERIALS AND METHODS

Materials

The equipment used in this study were analytical scales, stirring rods, glassware, glass jars, dropper pipettes, glass funnels, mortars, stamper, hot plates, pH meters, glass objects, 80 g loads, 100 g loads, rulers, stopwatch, glass, rotary evaporator and Design Expert® version 11 software program as data processor. The materials used in this study were simplicia of Tekelan leaves, n-hexane, 96% ethanol, aquades, triethanolamine (TEA), glycerin, carbopol, propylparaben, and methylparaben.

Methods

Extraction

Tekelan leaves macerated using 96% ethanol (1:10 part solvent) for 24 hours with two times re-maceration. The filtrate obtained was collected in one container and evaporated using a rotary evaporator with a temperature of 40-50°C.⁶

Dechlorophylation

The raw extract of TL was dissolved with 96% ethanol (1:10 part of the solvent). Then it was extracted using n-hexane (4:1 part of the extract).⁷ The n-hexane phase is discarded, and the ethanol phase is collected in a container.

Phytochemical screening

Phytochemical screening was carried out using a tube reaction consisting of alkaloid, flavonoids, saponins, and tannins.

Gel base formulation and optimisation

Formulas of the gel processed by the Design Expert data. Carbopol was swelled with hot water for 10 minutes (mass 1). In different containers, glycerin, metal parabens, and propyl parabens were mixed (mass 2). Mass one and mass two are mixed until

the homogeneous form was formed and then mixed with TEA, deodoriser and distilled water together to the desired volume. All of the gel bases which have been made are evaluated for the spreadability test, sticky power, and pH. The evaluation results are processed using Design-Expert version 11.

Formulation of TLE HSG

Gel hand sanitiser of TLE formulated based on the optimum formula. TLE concentration of 2.5% was added to the optimum gel base formula. The preparation of TLE HSG was evaluated for its physical properties in the form of the spreadability test, sticky power and pH. The spread test is carried out by placing 0.5 gram of gel on top of glass I, then placing another glass on it, left for 1 minute. Measured diameter produced by the distribution of the gel using a ruler. Measurements are periodically carried out by continuing to add loads up to 100 grams. Test the stickiness is done by clicking Apply gel on top of the glass objects already known extent. Put another glass object on the gel and then stacked with a load of 1 kg for 5 minutes. The object-glass is assembled at a weight of 80 g. Load 80 grams will be released until the two glass objects are separated. The time is taken until the two glass objects are separated recorded as the sticky power time of the gel preparation.

Comparative Test of TLE HSG

The evaluation result of the physical properties of TLE HSG is compared with the physical properties of commercial HSG circulating in the market. In addition to their physical properties, a comparative test was carried out on the acceptability test of both. Acceptability test was conducted on 20 volunteers using a questionnaire. Testing is done by asking for volunteer responses who try the TLE and commercial HSG. The response requested is in the form of colour, aroma, texture, and sticky impression.⁸ The acceptability conclusion can be seen from the percentage of values obtained by the following formula.⁹

RESULTS

HSG optimisation is done using the simplex lattice design method available in Design-Expert software version 11. Based on variations in the concentration of three ingredients (glycerin, TEA, and carbopol) and using two replications, the software recommends 13 gel-based formulas. Thirteen gel base formulas will be formulated manually and evaluated for their physical properties in response to obtaining the optimum formula. The results of

Table 1 The results of the evaluation of the response of spreadability, sticky power and pH

Run	The response		pH
	Spreadability (cm)	Stickiness (seconds)	
1	2.70	1.05	7.6
2	6.43	0.47	7.3
3	3.28	1.85	7.4
4	4.63	0.64	7.5
5	3.25	1.00	7.2
6	2.50	0.53	7.3
7	3.30	0.86	7.5
8	3.13	0.50	7.3
9	4.78	0.50	7.3
10	4.30	0.49	7.4
11	2.75	0.92	7.5
12	4.73	0.47	7.6
13	2.63	1.03	7.3

Table 2 Optimal cream base formula data using software Design Expert® version 11

Name	Goal	Lower Limit	Upper Limit	Importance
A: Glycerin	in range	2.50	4.00	3
B: TEA	in range	0.50	2.00	3
C: Carbopol	in range	1.00	2.50	3
Spreadability	maximize	2.50	6.43	5
Stickiness	maximize	0.47	1.85	4
pH	minimize	7.20	7.60	5

Table 3 The SLD equation for each response for the gel base formula

The response	SLD equation
Spreadability	$Y = 5.52 (A) + 4.66 (B) + 2.62 (C) - 4.01 (A) (B) - 4.03 (A) (C) - 3.29 (B) (C) - 1.32 (A) (B) (C)$
Stickiness	$Y = 0.497 (A) + 0.523 (B) + 0.764 (C) - 0.240 (A) (B) - 0.555 (A) (C) + 0.726 (B) (C) + 28.30 (A) (B) (C)$
pH	$Y = 7.30 (A) + 7.55 (B) + 7.30 (C) - 0.081 (A) (B) + 0.019 (A) (C) + 0.319 (B) (C) + 21.41 (A B C)$

Note: Y= response; A= Glycerin concentration; B= TEA concentration; C= carbopol concentration

Table 4 Verification of optimum base formula

The response	Prediction	Trial	p-value	Conclusion
Spreadability (cm)	3.67	3.62 ± 0.21	0.65	No different
Stickiness (seconds)	1.18	1.10 ± 0.12	0.27	No different
pH	7.18	7.30 ± 0.08	0.07	No different

the measurements of the thirteen base formulas are presented in Table 1.

Based on the response value generated by each run, the researcher then determines the importance and goals of each response and material component. The importance and goals used for glycerin, TEA, and carbopol are the default values for the pair of software. The importance and goals values of each response are shown in Table 2. Based on the analysis and data processing with software Design Expert® version 11, it can determine equation SLD for each response as presented in Table 3.

The optimum gel base formula is verified by manually evaluating physical properties. The optimum formula can be said to be verified if there is no significant difference between the prediction of the software and the results of manual evaluation. Analysis of these differences, the statistical analysis of One sample t-test was used. One sample t-test analysis results can be seen in Table 4.

Furthermore, TLE phytochemical screening was performed on both extracts both before dechlorophyllation and after dechlorophyllation. The results of the phytochemical screening are shown in Table 5. The remade TLE gel formula in the evaluation of its physical properties includes a test of spreadability, sticky power, pH and acceptability.

Through Table 6, it is known that the addition of extracts affects the spread and sticky power response but does not affect the pH response. An increase in the dispersal power and a decrease in sticky power in the TLE hand sanitiser gel compared to the optimum gel base formula. The pH of the acidic extract influences these changes. The acidic pH of the extract results in a decrease in viscosity so that the gel's texture becomes more liquid. The viscosity of the sticky power decreases indirectly causing the impression of stickiness to be reduced. HSG preparations with low sticky impression tend to be more favoured by consumers.

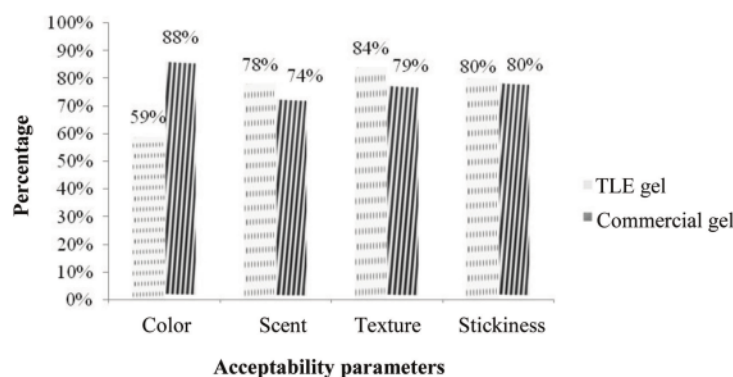
Finally, the acceptability test was done on the TLE HSG. Acceptability tests were also performed on commercial HSG as a comparison. This test was conducted to find out how much the preparation of TLE HSG made was acceptable to respondents as consumers. Acceptability tests were carried out on 20 respondents with acceptability parameters in the form of colour, aroma, texture, and sticky impression. Assessment is done in a range or score system of 1-5 where 1 represents the least likes and five means very like. The results of the respondents' assessment can be seen in the graph presented in Figure 1.

Table 5 Phytochemical screening results of TLE

Testing	Test result	
	Before de-chlorophyllation	After dechlorophyllation
Saponin	+	-
Flavonoids	+	+
Tannin	+	+
Alkaloids	+	-

Table 6 Results of the evaluation of the spreadability, sticky power and pH of TLE HSG

Evaluation	Results
Scattering	3.95 ± 0.46 cm
Stickiness	0.94 ± 0.05 seconds
pH	6.75 ± 0.33

**Figure 1** Results of TLE HSG acceptability test

DISCUSSION

Through the analysis that has been done based on acceptability data, TLE HSG can be well received by respondents with a percentage of acceptance of 75.25%. The percentage of acceptance of TLE HSG was slightly lower compared to commercial HSG, which had an acceptance percentage of 80.25% or were stated to be in the "very good" category.

The higher the importance value, the higher the importance of the response. The dispersion and pH response was chosen with the highest importance because the ability to spread the preparation and its pH compatibility with the skin were the most important parameters.¹⁰ Goal setting is based on the expected response value.

Spreadability is one of the important parameters in making topical preparations. Spreadability is a response parameter that describes the ability to spread a topical preparation to the skin. According to Garg (2002), the spreadability for semisolid

preparations is divided into two, namely semi-stiff and semifluid. In the semistiff, the specified distribution power is 3-5 cm, while for the semifluid is 5-7 cm.¹¹

Sticky power response illustrates the ability of a topical preparation, in this case, is an HSG to adhere to the surface of the skin. The higher ability of the preparation to stick to the surface of the skin allows the active substance to provide a longer-lasting biological effect. Sticky power is directly proportional to the texture of the thickness of the preparation.¹² In pharmaceutical preparations with a topical administration route, pH is a response parameter that chemically must have compatibility with the surface conditions of the skin. In the formulation of this study, TEA is a material that is responsible for maintaining pH stability as well as being useful in adjusting pH. The pH of the preparation must be in the range of 6.0-7.0 to prevent skin irritation.¹³

Results of the equation show the influence of each component and interaction factors on the value of the spread, stickiness and pH. A positive sign (+) in the equation indicates that the component increases the response value (spreadability, sticky power, and pH). Vice versa, the negative sign (-) in the equation shows that the component can reduce the value of the spreadability, sticky power and pH.

Based on the results of data analysis, the optimum formula composition obtained from Design Expert® version 11 software was 1.860% glycerin, 2.90% TEA and 0.739% carbopol. As for predictions response dispersive power of 3.673 cm, the power response engrossed t of 1.181 seconds and the response of the pH of 7.187.

Based on Table 4, it can be seen that the p-value is greater than 0.05. So the results of this verification ensure that optimisation with software can be accepted or verified. Tekelan leaves extract will be added with a concentration of 2.5% to the optimum base formula to obtain a preparation of TLE HSG. TLE was obtained from the simplicia of Tekelan leaves macerated with 96% ethanol for 3x24 hours, followed by dechlorophyllation using n-hexane solvent. Chlorophyll needs to be separated from thick extracts because it gives an unattractive appearance when the extract is formulated in pharmaceutical preparations. Also, chlorophyll causes green scars that are difficult to disappear when the formula containing the extract is applied to the surface of the skin.¹⁴

Based on the percentage of the number of respondents in Figure 1, it appears that the TLE HSG is superior to several acceptability test parameters. In

general, TLE HSG is superior in aroma, texture and sticky impression compared to commercial HSG. The fragrance used in the TLE HSG formulation is softer and has no pungent odour, so respondents prefer it. The texture and stickiness of the TLE HSG are also preferred over commercial HSG. This is because the texture of TLE HSG tends to be lighter and does not cause uncomfortable stickiness to the respondents.

In contrast, the TLE HSG is weak in colour parameters. The colours of TLE HSG are green like moss while commercial brands have attractive colours that are clear white and transparent. The results of this study are expected to be the initial data for further researchers to continue developing hand sanitisers from Tekelan leaves.

CONCLUSION

Based on the results of the study it can be concluded that the optimum formula for HSG base is a gel base with a glycerin concentration composition of 1.86%, TEA 2.90%, and carbopol 0.74%. HSG preparations of TLE which are formulated using optimum base formula have good physical properties with a spread response of 3.95 cm, adhesion 0.94 seconds, and a pH of 6.75. The percentage of acceptability of the HSG preparations of TLE was 75.25% while the commercial gel had a percentage of acceptability of 80.25% (very good category).

ETHICAL CLEARANCE

This study was approved by the Health Research Ethical Commission of Universitas Mataram with the ethical clearance number: 314/UN18.F7/ETIK/2019.

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CONFLICT OF INTEREST

This research was conducted to improve the knowledge without any conflict of interest.

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