International Journal of Basic & Clinical Pharmacology
Sari R et al. Int J Basic Clin Pharmacol. 2024 Sep;13(5):580-586
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20241943

Original Research Article

Formulation and effectiveness test of Tekelan leaf ethanol extract nanogel preparations against *Propionibacterium acnes*

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Received: 17 June 2024
Revised: 01 July 2024
Accepted: 02 July 2024

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ABSTRACT

Background: Ethanol extract of Tekelan leaves can inhibit the growth of *Propionibacterium acnes* bacteria. The nanogel preparation can penetrate the deepest layer of the stratum corneum. Utilization of Tekelan leaves in the form of nanogels that have better absorption capabilities with minimal side effects due to the use of natural ingredients is essential to be carried out as an alternative to anti-acne drugs.
Methods: This study was conducted experimentally, including the preparation of ethanol extract of Tekelan leaves and formulation in nanogel preparations, which were then tested for antibacterial activity. The concentration of ethanol extract of Tekelan leaves in nanogel preparations were 2.5%, 5%, and 7.5%.
Results: The organoleptic of nanogel containing ethanol extract of Tekelan leaves showed that the color was brown and had a distinctive odor, the preparation was homogen, viscosity was still in the required range, pH was still in the required range, 4.5-6.5. The size was below 200 nm, and the cycling test showed that they were stable during storage for six cycles. The nanogel preparations with concentrations of 2.5%, 5%, and 7.5% had diameter inhibitions of 7.93 mm, 9.10 mm, and 10.23 mm, respectively.
Conclusions: Based on the study's results, it can be concluded that the nanogel preparation of ethanol extract of tekelan leaves is stable during 12 weeks of storage and has a particle size below 200 nm. The antibacterial test results of nanogel preparations of ethanol extract of tekelan leaves at a concentration of 7.5% have the maximum activity.

Keywords: Tekelan leaf, Nanogel, Antibacterial

INTRODUCTION

Acne is an abnormal skin condition in which clogged pores lead to infection, resulting in inflamed pockets of pus. It is characterized by the appearance of spots on certain parts of the body, such as the face, neck, back, and chest.[1] Many factors, including genetics, age, cosmetics, hormones, food, stress, and bacteria, cause acne. *Propionibacterium acnes* are bacteria that cause acne blackhead formation.[2]

Acne is a skin health problem that affects adolescents and adults, with a prevalence of 80%.[3] Inflammation in acne can be triggered by pathogenic bacteria that can enter the host body in several ways, one of which is through open skin areas such as wounds, hair follicles, and sweat gland pockets.[4] *P. acnes* bacteria can cause infection in acne.[5]

Acne has been treated with oral and topical preparations such as antibiotics and retinoids for many years. However, antibiotic resistance, retinoid side effects, and drug

allergies are also increasing in dermatology treatment. To solve these problems, alternative treatments from medicinal plants have been widely studied to treat various diseases.[2] The use of traditional medicine is generally considered safer than the use of modern medicine. This is because traditional medicine has relatively fewer side effects than modern medicine.[6]

One of the herbal plants used to treat acne is Tekelan leaves. Tekelan is one type of plant from the Asteraceae family. Tekelan leaves contain several main compounds, such as tannins, flavonoids, saponins, alkaloids, and steroids.[7] Based on research by Hanphakphoom tekelan leaf extract has antibacterial activity against bacteria that cause infections on human skin. Based on Yuliani's research *C. odorata* is effective for healing incision wounds in Sprague dawley rats.[8,9]

Vijayaraghavan et al stated that the content of phytochemical compounds in *C. Odorata* L., including flavonoids including quercetin, sinersetin, sakuranetin, padmatin, kaemferol, salvagenin, and phenolic acids.[10] Researcher Nurwahidah stated that based on the results of isolation on the leaves of *C. Odorata* L., quercetin is one of the flavonoids. Odorata L. quercetin is the most abundant compound found in tekelan leaves.[11] Quercetin and its glycosides are in the amount of about 60-75% of flavonoids. Based on Rahmi's research the quercetin compound found in tekelan leaves has very strong antioxidant properties, namely 31.145 mcg/ml.[12] Quercetin is part of flavonoid compounds that act as antioxidants because it has a molecular structure containing phenolic hydroxy groups. Quercetin can also act as an enzyme inhibitor useful in forming free radical compounds such as xanthine oxidase, lipooxygenase, protein kinase-C and cyclooxygenase.[12]

One of the disadvantages of quercetin compounds in Tekelan leaf extract is its low water solubility and high permeability because it is included in the class 2 category based on the biopharmaceutical classification system (BCS).[13] In addition, the penetration properties of quercetin compounds are low, which makes it difficult to penetrate the stratum corneum layer, which consists of keratin and intracellular lipid layer.[14] To overcome the problem of quercetin present in Tekelan leaf extract, a new formula was made in the form of nanogels.

Cosmetic products using nanotechnology aim to create structures that can release poorly water-soluble ingredients. This will allow the release to be gradual, safe, and localized and improve skin penetration.[15] Nanogel formulas are designed to have good physical stability and use a gel base with a composition that can moisturize and increase safety.[16] Nanogel preparations can also increase the contact surface area so that bioactive delivery becomes faster and easier. The smaller particle size is expected to increase the contact area of particles with the membrane and make it easier for particles to penetrate the membrane.[17] Nanogels consist of various natural, synthetic polymers or combinations that encapsulate small molecular particles, oligonucleotides, and proteins. Three-dimensionally cross-linking polymer chains make nanogels with hydrophilic or amphiphilic macromolecules that are ionic or nonionic.[18]

Nanogels have better stability, exhibit lower critical micelle concentrations, slower dissociation rates, and longer retention of the loaded drug, and these delivery systems usually do not produce immunological responses. Nanogels can load hydrophilic, hydrophobic, and soluble drug types.[19] Nanogel formulations show an increase in the amount of drug accumulated on the epidermis up to 5 times compared to regular gel formulations. Thus, nanogels provide higher efficacy than gels, with drug distribution on a larger surface area due to the smaller particle size of nano size.[20]

Topical nanogels are very suitable for drug delivery systems as they are non-greasy, and easier to wash off the skin than ointments and creams. Instead of aiming for the drug to immediately redeem the skin surface, nanoparticles are equipped with a protective barrier from all exogenous factors such as viruses, allergens, dust, and bacteria, all of which are nano-sized.[21] Utilizing drugs in the form of nanoparticles to improve skin permeability is not based on nano-size but on other physicochemical properties of the drug, such as improved solubility, dissolution, charge protection, and enhanced contact for better absorption.[20]

Based on the description above, we interested in developing the use of Tekelan leaves to treat acne formulated into nanogel preparations, then tested the preparation's stability and antibacterial activity.

METHODS

Materials

The materials used in this study were Tekelan leaves, bacteria: *P. acnes*, distilled water, DMSO (Dimethyl sulfoxide), 96% ethanol (Emprove), carbopol 940 (Nipest 40), rabbit skin membrane, triethanolamine (Merck), tween 80 (Merck), propylene glycol (Dow), methylparaben (PT. Brataco, Medan), propylparaben (PT. Brataco, Medan), nutrient agar (NA), and nutrafor.

Nanogel formulation

The nanogel preparation formulation consisted of Tekelan leaf ethanol extract (2.5%; 5% and 7.5%), 70% ethanol, propylene glycol, tween 80, carbopol 940, methyl paraben, propyl paraben, triethanolamine, and distilled water. The ethanol extract of Tekelan leaves was used as an antibacterial ingredient against acne-causing bacteria. Tween 80 was a dispersing agent, stabilizer, and surfactant, propylene glycol served as a humectant, the gel base used is carbopol 940, methyl paraben and propylparaben as preservatives, triethanolamine was used to neutralize the carboxylic group of the polymer and

ionize, where electrostatic repulsion occurs between negatively charged particles to increase the development and thickening properties of the polymer (rigid). Nanogels were prepared using the polymer dispersion method. The ethanol extract of Tekelan leaves was weighed with various weight variations. Before formulation, carbopol was first developed in a mortar for 24 hours. The ethanol extract of Tekelan leaves weighed according to the concentration was stirred constantly with a magnetic stirrer at 1000 rpm for 15 minutes. Propylene glycol was added gradually, then stirred constantly with a magnetic stirrer at 1000 rpm for 1 hour (organic phase). Tween 80 was dissolved in distilled water in a different container and stirred constantly with a magnetic stirrer at 1000 rpm for 1 hour (water phase). The organic phase was added to the water phase by dripping little by little while stirring constantly with a magnetic stirrer at 2500 rpm for 2 hours. Then, the mixture was sonicated for 1 hour until nanodispersion was formed. Carbopol that has been developed was added to a mixture of methyl parabens and propyl parabens, which have dissolved and crushed until homogeneous. The carbopol and preservative mixture was transferred to a beaker glass container, stirred until homogeneous at 2500 rpm, and allowed to stand for 2 hours. Then TEA was added as much as 2 drops to form a gel base. The nanodispersion was added to the gel base and the remaining TEA while stirring constantly with a homogenizer at 1000 rpm for 30 minutes. After homogenization, sonication was carried out for 1 hour to form nanogels. pH and particle size measurements were taken.[22]

Table 1: Tekelan leaf ethanol extract nanogel formula.

Materials	NF 1	NF 2	NF 3
Leaf ethanol extract Tekelan (%)	2.5	5	7.5
Carbopol (g)	0.5	0.5	0.5
Tween 80 (ml)	3	3	3
Propylenglycol (ml)	4	4	4
Ethanol (ml)	10	10	10
Methyl paraben (g)	0.2	0.2	0.2
Propyl paraben (g)	0.02	0.02	0.02
TEA (ml)	0.3	0.3	0.3
Aquadest (ml)	Ad. To100	Ad. To100	Ad. To100

*NF: Nanogel formula

Evaluation of nanogels

Organoleptic test

Organoleptic examination in the form of shape, odor, and color was carried out visually from the nanogel preparation made.[23]

Homogeneity test

The homogeneity test was carried out by taking 0.25 grams of gel preparation, placing it on a glass plate, and covering it with another glass plate. The glass plate was pressed and rubbed to see and feel whether the preparation was flat or not.[24]

Viscosity measurement

Viscosity measurement was carried out with an NDJ-8S viscometer. The nanogel preparation was put into a 100 ml beaker glass and placed in a customized container. The spindle used for viscosity measurement was spindle 4, and the speed was set at 60 rpm because it was adjusted to the nanogel preparation. The viscometer was run, and the viscosity of the nanogel was observed and recorded.

Measurement of the pH of the preparation

The pH of the preparation was determined using a pH meter. The tool was first calibrated using a neutral pH (pH 7.01) and acidic pH (pH 4.01) dapar solution until the tool showed the pH price. Then, the electrode was washed with distilled water and dried with tissue. The pH test was carried out by weighing 1 gram of the preparation and then diluted with 10 ml of distilled water. Then, the calibrated pH stick was dipped for 1 minute. The pH value read on the device was recorded and repeated three times.[24]

Determination of particle size

Particle measurement was carried out with a Fritsch particle size analyzer (PSA). The particle measurement process was carried out by inserting the preparations into the tool until detected. Testing was carried out four times, namely after making the preparation, week 4, week 8, and week 12.

Physical stability study of nanogels

The *cycling test* method was carried out by storing the preparation at two different temperatures in 6 cycles. The nanogel preparation was put into a closed container. Then, the sample was stored in a refrigerator at 4ºC for 24 hours and then transferred to an oven with a temperature of 45º±2ºC for 24 hours. This treatment was one cycle, and the treatment was repeated for six cycles. After that, the organoleptic condition of the preparation (shape, color, odor, and phase separation) was observed. The physical condition of the preparation was compared before and after the cycling test.

Antibacterial activity testing of Tekelan leaf ethanol extract nanogel

Antibacterial activity testing was carried out on Tekelan leaf ethanol extract nanogel with various concentrations and compared with the existing preparation on the market (Nutrafor acne gel). This test was conducted using the agar diffusion method. A total of 0.1 mL of inoculum was put into a sterile Petri dish, after which 15 mL of Nutrient Agar (NA) media was poured at a temperature of 45-50 ℃. The cup was shaken on the table surface so that the media and

bacterial suspension were evenly mixed and solidified. Each petri dish is placed on a paper plate dripped with a nanogel test solution of ethanol extract of Tekelan leaves. Then, it was incubated at 36-37°C for 24 hours, and the diameter of the inhibition zone was measured with a caliper expressed in millimeters. The test was conducted with 3 repetitions.[25]

RESULTS

The results of nanogel formulations were blackish brown, slightly viscous, and had a distinctive aroma (Figure 1).

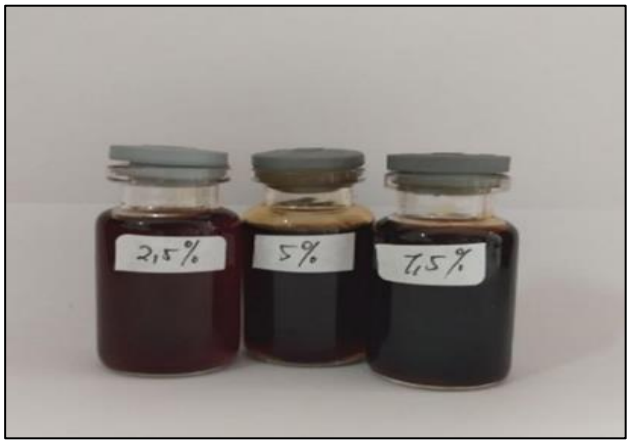

Figure 1: Nanogel formulation.

Evaluation of nanogels

Organoleptic test

Organoleptic examination results were performed on all dosage formulas and evaluated immediately after completion. Organoleptic tests were observed visually on all formulas, including color, odor, and shape. Organoleptic results can be seen in Table 2.

Table 2: Nanogel formulation results.

Formula	Color	Shape	Odor
NF 1	Brown	Transparent	Typical
NF 2	Dark brown	Transparent	Typical
NF 3	Blackish brown	Transparent	Typical

*NF: Nanogel formulation

The organoleptic results of nanogel concentrations of 2.5%, 5%, and 7.5% were brown, dark brown, and blackish brown, respectively, had a distinctive aroma of tekelan leaves, and were transparent.

Homogeneity test

The purpose of homogeneity was to determine the homogeneity aspect of nanogels. The results of the homogeneity test can be seen in Table 3.

Table 3: Nanogel homogeneity check results.

Formula	Homogeneity
NF 1	Homogen
NF 2	Homogen
NF 3	Homogen

*NF: Nanogel formulation

Viscosity measurement

Viscosity measurement aims to determine preparation's viscosity so it can flow. Viscosity measurement using Brookfield NDJ-85 (Table 4).

Table 4: Nanogel viscosity measurement results.

Formula	Viscosity (mPa.s)
NF 1	3891.33±1.52
NF 2	4342.66±0.57
NF 3	4565.33±2.08

*NF: Nanogel formulation

The viscosity value expresses the amount of resistance a liquid has to flow. The higher the viscosity value, the greater the resistance to flow. Carbopol is one type of gelling agent that provides excellent stability when in a neutral pH atmosphere, resulting in the preparation's viscosity not shifting and remaining stable.

pH measurement

The pH measurement was carried out to determine the pH of the nanogel preparation by the skin, because the preparation will be in direct contact with the skin and affect the skin condition (Table 5).

Table 5: Results of pH measurement for nanogels.

Formula	pH
NF 1	4.80±0.01
NF 2	4.70±0.01
NF 3	4.60±0.01

*NF: Nanogel formulation

From the above results, it can be seen that during storage, all nanogel preparations of ethanol extract of Tekelan leaves stored at room temperature for 12 weeks showed a slight decrease in pH so that the pH value produced still meets the pH requirements of the skin, namely pH values in the interval 4.5-6.5.

Particle size measurement

Particle size measurements were carried out at the nanomedicine laboratory, faculty of pharmacy, universitas Sumatera Utara using the FRITSCH analysette 22 NanoTes PSA at room temperature. The average results of nanogel particle size measurements and the graph of changes in nanogel particle size influenced by the length of storage can be seen in Table 6.

Table 6: Nanogel particle size results.

Formula	Particle size (nm)
NF 1	164.36±0.40
NF 2	171.18±0.79
NF 3	180.49±0.13

*NF: Nanogel formulation

Based on the particle size analysis results, during 12 weeks of storage, all formulated Tekelan leaf ethanol extract nanogels experienced an increase in particle size. The increase in particle size is still within the range of nanometer particle size requirements, so all Tekelan leaf ethanol extract nanogels can be said to be stable in nanogel preparations. During 12 weeks of measurement, it can be concluded that the average size of the tekelan leaf ethanol extract nanogel meets the size requirements, which does not exceed 1000 nm from the beginning of formulation to 12 weeks of storage.[28]

Cycling test stability study

Cycling test observations were made on the Tekelan leaf ethanol extract nanogel preparation which was stored at 4±2 °C in the refrigerator for 24 hours and then transferred and stored at 40±2°C in a climatic chamber for 24 hours, this treatment was counted as one cycle. The cycling test method was repeated for six cycles, then the physical condition of the nanogel preparation was observed by comparing the preparation before and after treatment. Data on the results of the cycling test of nanogel preparation of ethanol extract of tekelan leaves can be seen in Figure 2.

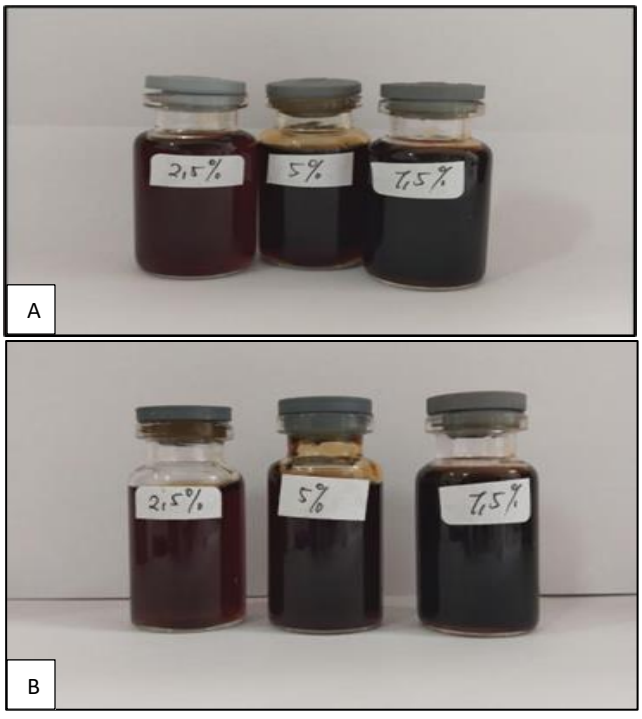

Figure 2 (A and B): Cycling test results of nanogel preparation of ethanol extract of tekelan leaf before storage and after storage.

Anti-bacterial activity

Testing the antibacterial activity of the Tekelan leaf ethanol extract nanogel preparation using the agar diffusion method; this method was used because it allows the nanogel preparation test material to be directly in contact with the walls of the agar media so that measuring the diameter of the inhibition zone will be easier and can be seen visually.[29]

Data from the diameter of the inhibition of *P. acne*s bacterial growth against the nanogel preparation of ethanol extract of tekelan leaves can be seen in Table 7.

Table 7: Bacterial diameter measurement results.

Formula	Obstacle zone
NF 1	7.93±0.115
NF 2	9.10±0.173
NF 3	10.23±0.153

*NF: nanogel formulation

Based on the table above, it can be seen that the higher the concentration of tekelan leaves used, the greater the inhibition produced. The quercetin contained in Tekelan leaves may play a role as an anti-bacterial, especially against bacteria that cause acne. Table 6 also shows that at a concentration of 7.5%, the nanogel has more significant inhibition.

DISCUSSION

The results of the homogeneity examination of the F1, F2, and F3 nanogel preparations showed that the nanogel preparation of ethanol extract of tekelan leaves was homogeneous before and after storage. Homogenous distributed active ingredients will maximize the release of active compounds on the skin.[23]

All formulas showed that the pH after adding the extract was getting smaller. This is due to the acidic pH of the extract (4.11). After storage for 12 weeks, the pH of all preparations decreased slightly but still met the skin pH requirements.[26,27]

Based on the results of particle size analysis, during 12 weeks of storage, all formulated tekelan leaf ethanol extract nanogels experienced an increase in particle size. The increase in particle size that occurred was still within the range of nanometer particle size requirements, so all Tekelan leaf ethanol extract nano gels can be said to be stable in nano gel preparations. During 12 weeks of measurement, it can be concluded that the average size of the tekelan leaf ethanol extract nanogel meets the size requirements, which does not exceed 1000 nm from the beginning of formulation to 12 weeks of storage.[28]

The cycling test to determine the stability showed that all nanogels of ethanol extract of Tekelan leaves showed no change in color, odor, or consistency. This indicates that

the nanogel preparation of ethanol extract from Tekelan leaves is physically stable.[29]

The formula 1 was able to inhibit the growth of *P. acnes* bacteria by 7.93 mm. In formula 2, the preparation inhibited the growth of *P. acnes* by 9.10 mm. In formula 3, the preparation inhibited the growth of *P. acnes* bacteria by 10.23 mm. The inhibition may be due to the presence of quercetin in the preparations.[30]

In this study the minimum inhibitory concentration of the extract inhibiting *P. acnes* bacteria growth was determined. However, the minimum inhibitory concentration value was only tested on *P. acnes* bacteria.

CONCLUSION

It can be concluded that Tekelan leaf extract can be formulated into nanogel preparations, were stable during the cycling test, and had particle sizes below 200 nm. Nanogel preparation F3 has the best antibacterial activity of 10.23±0.153.

ACKNOWLEDGEMENTS

Authors would like to thank Department of Pharmaceutics and Pharmaceutical Technology, Department of Pharmacology and Clinical/Community Pharmacy, Faculty of Pharmacy, Universitas Sumatera Utara.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Kusbianto D, Ardiansyah R, Hamadi DA. Impelementasi Sistem Pakar Forward Chaining untuk Identifikasi dan Tindakan Perawatan Jerawat Wajah. Jurnal Informatika Polinema.2017;4(1):71-80.
2. Baisaeng N, Klayraung S. *In Vitro* Antibacterial Activity of Hydrogels Containing Tamarind Seed Husk Extracts against *Propionibacterium acnes*. Trans Tech Publications. 2019;819:85-91.
3. Arshdeep dan De D. Whats new in the management of acne? Indian J Dermatol Venereol Leprol. 2013;79(3):279-87.
4. Pratiwi ST. Mikrobiologi Farmasi. Jakarta: Penerbit Erlangga. Halaman. 2008;12:176-7.
5. Wasitaatmadja SM. Penuntun Ilmu Kosmetik Medik. Jakarta: Penerbit UI-Press. Halaman. 1997;59-60.
6. Bustanussalam. Pemanfaatan Obat Tradisional (Herbal) Sebagai Obat Alternatif. BioTrends. 2016;7(1):20.
7. Yenti R, Afrianti R, Dan Sandi M. Uji Efektivitas Krim Ekstrak Etanol *Euphatorium odoratum* (L) Terhadap Kerapatan Serabut Kolagen Pada Proses Penyembuhan Luka. SCIENTIA. 2013;3(1):11-6.
8. Hanphakphoom S, Thophon S, Waranusantigul P, Kangwanrangsan N, Krajangsang S. Antimicrobial Activity of Chromolaena odorata Extracts againts Bacterial Human Skin Infections. Modern Applied Sci. 2016;10(2):159-71.
9. Yuliani NS. Efek Ekstrak Etanol Daun (Chromolaena odorata) Terhadap Kesembuhan Luka Insisi pada Tikus Sprague Dawley. Tesis. Yogyakarta: Program Studi Sain Veteriner. Universitas Gadjah Mada. Halaman. 2012;8-10.
10. Vijayaraghvan K, Rajkumar J, Syed BNA, Syed MA. Chromolaena odorata: A Neglected Weed a Wide Spectrum of Pharmalogical Activities (Review). Mol Med Rep J. 2017;3(2):1007.
11. Nurwahidah. Analisis Nilai Absorbansi dalam Penentuan Kadar Flavonoid Hasil Ekstraksi Daun Kopasanda (*C. odorata*). Tesis. Makasar: Universitas Islam Negeri Alauddin. Program Magister Sains. Fakultas Sains dan Teknologi. Hal. 2021;53-5.
12. Rahmi S. Formulasi Etosom Ekstrak Etanol Daun Tekelan (*Chromolaena odorata L.*) dan Karakterisasi Fisik, Uji Stabilitas Fisik, Penetrasi serta Aktivitas Anti Penuaan Kulit secara *In Vivo*. Disertasi. Medan: Universitas Sumatera Utara. Program Studi Doktor Ilmu Farmasi. Fakultas Farmasi. 2024.
13. Rahman VR, Dan Arif B. Improving the Permeability of BCS Class II, III, IV Drugs Using The Co-Amorph Method. Article Rev. 2023;6(1):307-14.
14. Suwalie ER, Dan Mita SR. Terpen Sebagai Peningkat Penetrasi pada Sediaan Transdermal. Farmaka. 2017;15(1):102-10.
15. Mitkare SS, Bangale MS, Gattani SG, Dan Sakarkar DM. Recent Nanotechnological Aspects in Cosmetics and Dermatological Preparations. Int J Pharm Pharmaceut Sci. 2012;4(2):88.
16. Chandrashekhar B, Anitha M, Ruparelia M, Vaidya P, Aamir R, Shah S, et al. Tretinoin Nanogel 0.025% Versus Conventional Gel 0,025% in Patients with Acne Vulgaris: A Randomized, Active Controlled, Multicentre, Parallel Group, Phase IV Clinical Trial. J Clin Diagnostic Res. 2015;9(1):4-9.
17. Thassu D, Deleers M, Pathak Y. Nanoparticulate Drug Delivery Systems. USA: Informa Healthcare. 2007.
18. Yin Y, Hu B, Yuan X, Cai L, Gao H, Yang Q. Nanogel: A Versatile Nano-Delivery System For Biomedical Applications. Pharmaceut. 2020;12(3):290.
19. Agarwal G, Pradip KK, Agarwal G. Semi-Herbal Nanogel of Clindamycin Phosphate and Aloe vera: Formulation and Evaluation. Mod Appl Bioequiv Availab. 2017;2(5):1-5.
20. Chavhan SS, Petkar CK, Sawant KK. Nanosuspensions in Drug Delivery: Recent advances, patent scenarios, and Commercialization Aspect. Crit Rev The Drug Carrier Syst. 2011;28(5):447-88.
21. Prow TW, Grice JE, Lin LL, Faye R, Butler M, Becker W, et al. Nanoparticles and microparticles for skin drug delivery. Adv Drug Deliv Rev. 2011;63(6):470-91.

22. Pranuti S, Prasanna V. Design and Development of Nanogels Containing Carbapol as Polymer and Hydroalcoholic Extract of Pterocarpus marsupium as Herbal Medicament. World J Pharmaceutical Res. 2018;7(19):790-801.
23. Ariyani LW, Dan W. Stabilitas Fisik Nanogel Minyak Zaitun (*Olea europaeae)*. J Ilmiah Cendekia Eksakta. 2020;5(2):101-8.
24. Naibaho OH, Yamlean PVY, Dan Wiyono W. Pengaruh Basis Salep terhadap Formulasi Sediaan Salep Ekstrak Daun Kemangi (Ocimun sanctum L.) pada Kulit Punggung Kelinci yang dibuat Infeksi *Staphylococcus aureus*. PHARMACON J Ilmiah Farmasi. 2013;2(2):27-34.
25. Harahap NI. Uji Aktivitas Antibakteri Gel Ekstrak Etanol Daun Sambung Rambat (Mikania micrantha Kunth) Terhadap Angiogenesis Luka Eksisi Terinfeksi Pada Marmut. Tesis. Medan: Program Studi Magister Farmasi Universitas Sumatera Utara. 2017.
26. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. Edisi Keenam. London: Pharmaceutical Press. Halaman. 2009;55:441-2.
27. Tranggono RI, Dan Latifah F. Buku Pegangan Ilmu Pengetahuan Kosmetik. Editor: Joshita Djajadisastra. Jakarta: Pustaka Utama. Hal. 2007;118-25.
28. Muniraj S, Yogananda R, Nagaraja T, Bharathi D. Preparation and Characterization of Nanogel Drug Delivery System Containing Clotrimazole an Anti-Fungal Drug. Indo Am J Pharmaceutical Res. 2020;10(7):1013-22.
29. Jawetz E, Melnick JL, Dan Adelberg EA. Mikrobiologi Kedokteran. Jakarta: Penerbit Salemba Medika. Halaman. 2005;26-31.
30. Herslambang RA, Dina R, Dan Mia F. Aktivitas Sediaan Gel Kuersetin Terhadap *Staphylococcus epidermidis.* GALENIKA. J Pharm. 2015;1(1):59-64.

Cite this article as: Sari R, Reveny J, Salim E. Formulation and effectiveness test of Tekelan leaf ethanol extract nanogel preparations against *Propionibacterium acnes.* Int J Basic Clin Pharmacol 2024;13:580-6.