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THE EFFECT OF KATUK LEAF GEL EXTRACT AS AN ANTI-INFLAMMATORY ORTHODONTIC TREATMENT ON CARRAGEENAN-INDUCED PAW EDEMA IN RATS

(*PENGARUH GEL EKSTRAK DAUN KATUK SEBAGAI ANTIINFLAMASI PERAWATAN ORTODONTI TERHADAP EDEMA KAKI TIKUS YANG DIINDUKSI KARAGENAN*)

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ABSTRACT

Katuk leaf herbal plants can be used as an anti-inflammatory drug because these contain flavonoids which be able to reduce inflammation by inhibiting cyclooxygenase enzyme formation. Katuk leaf extract is made in gel form at a 78.3 mg/kg BW dose. The gel is one of the medicinal preparations with good dispersion and longer adherence ability compared to ointments and creams. The study aimed to determine the effect of Katuk leaf extract gel as an anti-inflammatory orthodontic treatment against carrageenan-induced rat leg edema. This type of laboratory experimental research used a posttest-only control group design. This study used Katuk leaf extract gel in the treatment group and

base gel for the control group, which was repeated 16 times in Wistar rat test animals in each group. The Independent variable is gel leaf Katuk extract, and volume-bound swelling on the soles of rats feet is the dependent variable—univariate and bivariate data analysis with the Mann-Whitney test. The study showed no significant difference in the average edema between the control and treatment groups; Katuk leaf extract gel had no effect on an edema volume (p-value=0.12) compared to the control group. The conclusion is that Katuk leaf extract gel does not reduce swollen volume compared to Na-CMC 0.5%.

Keywords: anti-inflammatory; edema; flavonoids; katuk leaf

ABSTRAK

Tanaman herbal daun katuk dapat digunakan sebagai obat antiinflamasi, karena mengandung flavonoid yang dapat menurunkan inflamasi dengan cara menghambat keluarnya enzim siklooksigenase. Ekstrak daun katuk dibuat dalam bentuk gel dengan dosis 78.3 mg/kgBB karena gel merupakan salah satu sediaan obat yang memiliki daya sebar baik dan kemampuan melekat yang lebih lama jika dibandingkan dengan obat sediaan salep dan krim. Tujuan dari penelitian yaitu untuk mengetahui pengaruh gel ekstrak daun katuk sebagai anti inflamasi perawatan ortodonti terhadap edema kaki tikus yang diinduksi karagenan. Penelitian ini merupakan penelitian eksperimental laboratorium dengan post-test only control group design. Penelitian ini menggunakan gel ekstrak daun katuk pada kelompok perlakuan dan basis gel untuk kelompok kontrol yang dilakukan pengulangan sebanyak 16 kali pada hewan uji tikus wistar di setiap kelompoknya. Variabel bebas gel ekstrak daun katuk dan varibel terikat volume bengkak pada telapak kaki tikus. Analisis data univariat dan bivariat dengan uji Mann Whitney. Hasil penelitian adanya perbedaan rata-rata edema yang tidak bermakna antara kelompok kontrol dan perlakuan, tidak terdapat pengaruh gel ekstrak daun katuk terhadap volume edema (nilai p=0.12) dibandingkan kelompok kontrol. Kesimpulan gel ekstrak daun katuk

tidak berpengaruh terhadap penurunan volume bengkak dibandingkan dengan Na-CMC 0.5%.

Kata kunci: *antiinflamasi; daun katuk; edema; flavonoid; gel*

INTRODUCTION

Malocclusion is a condition of abnormal occlusion caused by an abnormal relationship between the growth and position of the maxillary and mandibular teeth.[1,2] Malocclusion is one of the third most significant dental and oral health problems, according to the World Health Organization (WHO).[3] The prevalence of dental and oral health problems, including Malocclusion in Indonesia in 2013 was 25.9% and increased to 57.6% in 2018.[4,5] Dayataka et al. 2018 reported that the prevalence of Malocclusion in adolescents aged 12-15 years in the city of Cimahi it reached 96.7%, this figure was higher than the prevalence of Malocclusion in the Jember area which was 91.6%.[6,7] The causes of Malocclusion are sometimes challenging to avoid because Malocclusion is a disorder caused by hereditary factors.[8,9] Malocclusion can cause a decrease in oral cavity function, and the emergence of aesthetic problems that can affect a person's quality of life and psychosocial conditions. will increase.[9,10,11]

Orthodontic treatment can be provided using orthodontic appliances. Orthodontic appliances are divided into 2, namely fixed orthodontic appliances and removable orthodontic appliances. Fixed or removable orthodontic appliance components can cause trauma to the soft and hard tissues in the oral cavity.[12,13] Trauma due to the use of orthodontic appliances can occur due to several reasons, namely excessive pressure from the appliance, abrasions between the mucosal surface and the rough base of the orthodontic appliance, and sharp appliance components.[14] Tissue trauma due to orthodontic appliances can trigger an inflammatory response.[15] Inflammation that occurs will be accompanied by swelling and pain, one of the signs of inflammation in the tissue.[13]

Inflammation of the tissues can cause the patient to feel pain and discomfort, which can be quickly treated by using chemical anti-inflammatory drugs.[16,17] Steroid and non-steroidal anti-inflammatory drugs can reduce

inflammatory reactions. Still both drugs have dangerous side effects, including ulcers in the digestive tract, decreased immune systems, and osteoporosis. Hence, we need alternative ingredients that can be used as anti-inflammatory drugs that cause fewer side effects.[18,19] One of the natural ingredients that can be used as an anti-inflammatory is Katuk leaves.[20]

Katuk leaves (*Sauropus androgynus L. Merr*) grow a lot and are widespread in Indonesia, Katuk leaves grow and are easy to find in areas at the foot of mountains and highlands.[21] Katuk plants can be used as natural ingredients to make anti-inflammatory drugs because they have compounds active flavonoids.[22] The anti-inflammatory effect caused by flavonoid compounds in Katuk leaves occurs by inhibiting the process of forming cyclooxygenase enzymes.[23] Pramitaningastuti et al., in 2017, also reported that the flavonoid content in Katuk leaves can overcome inflammatory reactions by interfering with releasing cyclooxygenase enzymes.[24] The cyclooxygenase enzyme can convert arachidonic acid into prostaglandins, reducing the dilation process of blood vessels so thet the swelling volume due to inflammation will also decrease. [25,26]

Research conducted by Desnita et al. in 2018 reported that Katuk leaf extract has relatively the same effectiveness as diclofenac sodium. Katuk leaf extract in patch form can also inhibit the inflammatory process with a percentage reaching 66.67-100%.[27] Herawati H et al., in 2021, reported that the ethanol extract of Katuk leaves at a dose of 78.3 mg/kg BW is optimal for increasing osteoblast cells.[28]

METHOD

This research was conducted after obtaining approval from KEP (Research Ethics Commission) Universitas Padjadjaran with ethical approval number NO: 274/UN6.KEP/EC/2023. This research is a type of True Experimental design research with a posttest-only control group design. The sampling technique in this study was carried out by simple random sampling. The selected sample must meet the inclusion criteria and not meet the exclusion criteria with the Wistar rat (Rattus norvegicus) research object. The inclusion criteria for the research object included male Wistar rats, body weight 150-250 grams, aged 8-12 weeks, had no anatomical abnormalities on the paws of the rats, came from the same farm and feed, and were in good health with characteristics of appetite. The Wistar eat well, their hair does not fall out, and they are active. Exclusion criteria included mice that experienced a 10% weight loss, rats whose behaviour turned

passive, and mice that died during the study. The number of samples in this study was 32, divided into two groups, namely the treatment and control groups. The two groups would be injected with carrageenan first sub plantarly, the treatment was smeared with Katuk leaf extract gel and the control group was smeared with 0.5% Na-CMC gel.

The volume of edema in the rat's feet was measured every 1 hour for 8 hours after being treated using a pletismometer at the Pharmacology and Therapeutic Laboratory, Faculty of Medicine, Padjadjaran University. The data that has been collected will then be analyzed using the SPSS program.

The analysis in this study consisted of descriptive analysis to describe the average volume of edema according to hours of treatment and a normality test using the Shapiro-Wilk test to determine the normality of the data mann-Whitney test to determine the average difference in edema volume of all treatment groups.

RESULT

Oedema volume measurement

In Table 1, the initial volume in the treatment group was as large as the increase in the control group four hours after treatment, which was 2.11 mm^3. Meanwhile, in the treatment group, it occurred three hours after treatment, namely 1.20 mm^3. The smallest average volume of edema after 1 hour of treatment occurred in the treatment group that received Katuk leaf extract gel of 1.12 mm^3 and in the control group of 0.91 mm^3.

Table 1. Average volume of edema according to treatment hours

Treatment	Average	SD
Volume before treatment		
Control	0.68	0.10
Treatment	0.61	0.07
1 hour of treatment		
Control	1.12	0.14
Treatment	0.91	0.07
2 hours of treatment		
Control	1.44	0.15
Treatment	1.20	0.12
3 hours of treatment		
Control	1.80	0.15
Treatment	1.15	0.14
4 hours of treatment		
Control	2.11	0.27
Treatment	1.06	0.14
5 hours of treatment		
Control	2.08	0.25
Treatment	0.97	0.11
The difference in 4 and 5 hours of treatment		
Control	0.03	0.03
Treatment	0.09	0.01

Table 2. Test the average difference of all treatment groups

Treatment	Average	SD	P value
Control	0.03	0.03	0.12
Treatment	0.09	0.01	

Results Table 2 showed no significant difference in the average change in edema volume between the treatment and control groups, as indicated by the value of p=0.12 (p>0.05). However, the most

significant change occurred in the treatment group that received Katuk leaf extract gel.

Figure 1. The volume of rat feet after 8 hours of treatment. **(A)**Treatment group **(B)**Control group.

DISCUSSION

Inflammation is a complex body response that can occur due to injury or tissue damage that sharp or blunt objects can cause.[29] Inflammatory responses can occur involving the vascular system in the tissues. The occurrence of inflammation aims to repair damaged tissue and destroy the cause of inflammation.[30] The inflammatory process can occur due to forming inflammatory mediators, namely prostaglandins, due to the cyclooxygenase enzyme. Cyclooxygenase enzymes are divided into cyclooxygenase-1 and cyclooxygenase-2, which have a role in the first and second steps in synthesizing or forming prostaglandin mediators.[31] Arachidonic acid into prostaglandin E2 (PGE2), which can cause vasodilation of blood vessels resulting in the formation of an edema or swelling as a sign of inflammation.[32]

The results of this study indicate that the ethanol extract gel of Katuk leaves proved to be ineffective in reducing the volume of swelling in the feet of carrageenan-induced mice, which was characterized by a p-value obtained from comparing the groups given Katuk leaf extract gel and gel base which reached several 0.12 ($p>0.05$) which means there is no significant difference between Katuk leaf extract gel and 0.5% Na-CMC gel base. Katuk leaves contain flavonoid phytochemical compounds that can stop the formation of substances that can cause an inflammatory reaction.[33,34] Flavonoids have anti-inflammatory abilities because they can reduce prostaglandin production caused by inhibiting of arachidonic acid metabolism due to decreased production of cyclooxygenase enzymes.[23,35]

The results of this study are different from research by Desnita et al. in 2018 which reported that the ethanol extract of Katuk leaves at a dose of 400 mg/kg BW in the form of a patch has anti-inflammatory activity with a percentage of inflammatory inhibition reaching 66.67-100%, and this can occur because there is a minor difference in the dose used in this study.[27] Istiqomah NA et al., in 2022, also reported that the effective dose as an anti-inflammatory is 450 mg/kg BW.[36] Based on the research that has been done, researchers

suggest that further studies needs to be done by increasing the dossage of Katuk leaf gel extract to 400-450 mg/kg BW to determine the effectiveness of katuk leaf extract gel as an anti-inflammatory.

Flavonoids as anti-inflammatory can be obtained from Katuk leaf extract by maceration method.[33] The Maceration method is a simple extraction method that does not use heat energy to avoid damaging to flavonoid compounds, which can be damaged if exposed to heat. Mix Katuk leaf plant powder and 96% ethanol solvent in a closed container media and store at room temperature.[37] Concentrated ethanol has selective properties, is non-toxic, and has high absorption and filtering capabilities. Therefore, 96% ethanol solvent can filter nonpolar and polar compounds.[38] 96% ethanol has lower polar properties when compared to 70% ethanol, so the use of 96% ethanol in making Katuk leaf extract can cause the total flavonoids to decrease. Dissolved is higher than the 70% solvent. It happened because flavonoids can dissolve better in low to moderate-polarity solvents.[39]

The inflammation that occurred in this study was an acute inflammation caused by carrageenan.[34] Carrageenan compounds in seaweed, namely red algae (*Rhodophyceae*), which are plants that produce carrageenan compounds.[40] Carrageenan can cause inflammation in mice which induces the formation of TNF-α. Inflammation caused by carrageenan resulted in several things happening, namely increasing the process of making prostaglandins and cyclooxygenase-2 enzymes, improving blood vessel permeability, and resulting in the formation of edema on the rat paw.[34]

CONCLUSION

Based on the results of the research that has been done, it can be interpreted that there is no effect of Katuk leaf ethanol extract gel at a dose of 78.3 mg/kgBW as an anti-inflammatory in orthodontic treatment on carrageenan-induced paw edema in the rat.

CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this research journal.

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REFERENCES

1. Wahyuningsih S, Hardjono S, Suparwitri S. Perawatan maloklusi angle klas I

dengan gigi depan crowding berat dan cross bite menggunakan teknik begg pada pasien dengan kebersihan mulut buruk. Maj Kedokt gigi Indones. 2014;21(2):204–11.

2. Virtika Ayu K, Hidajah N, Walianto S. Analisis thompson & brodie pada kasus gigitan dalam. IJKG [Internet]. 2022;18(1):56–61. Available from: https://e-journal.unmas.ac.id/index.php/interdental
3. Lombardo G, Vena F, Negri P, Pagano S, Barilotti C, Paglia L, et al. Worldwide prevalence of malocclusion in the different stages of dentition: A systematic review and meta-analysis. Eur J Paediatr Dent. 2020;21(2):115–112.
4. Kemenkes RI. Riset Kesehatan Dasar Tahun 2013. Vol. 7, Kementrian Kesehatan RI. 2013.
5. Kemenkes RI. Hasil Riset Kesehatan Dasar Tahun 2018. Vol. 53, Kementrian Kesehatan RI. 2018.
6. Dayataka RP, Herawati H, Darwis RS. Hubungan tingkat keparahan maloklusi dengan status karies pada remaja di smp negeri 1 kota cimahi. Padjadjaran J Dent Res Student. 2018;2(1):1–7.
7. Lailatul F, Sutjiati R. Kebutuhan perawatan ortodonsi siswa sekolah dasar sumbersari v kecamatan sumbersari kabupaten jember dengan menggunakan indeks handy capping malocclusion assessment record (hmar). Stomatognatic (JKG Unej). 2013;10(1):47–50.
8. Aditya MY, Baehaqi M, Sri Praptiningsih R. Pengaruh pengetahuan orang tua tentang ortodonsi preventif dengan perilaku pencegahan maloklusi pada gigi anak. Odonto Dent J. 2015;2(1):46–50.
9. Arifin R, Sunnati SK. Dampak maloklusi gigi anterior protrusif terhadap status psikososial remaja usia 15-17 tahun menggunakan indeks pidaq (Studi Pada 4 Sman Banda Aceh). Cakradonya Dent J. 2016;8(2):132–8.
10. Arifin R, Herwanda, Tefani CR. Hubungan penilaian persepsi estetika oral dengan keadaan maloklusi menggunakan oral subjective index scale (OASIS) dan dental aesthetic index (DAI) (studi pada remaja usia 16-17 ahun di sman kita banda aceh). Cakradonya Dent J. 2018;10(1):10–7.
11. Elyaskhil M, Shafai NAA, Mokhtar N. Effect of malocclusion severity on oral health related quality of life in Malay adolescents. Health Qual Life Outcomes [Internet]. 2021;19(1):1–5. Available from: https://doi.org/10.1186/s12955-021-01710-2

12. Ossa YF, Ulfah K, Sİtİnjak RR. Treatment of traumatic ulcer induced by fixed orthodontic appliance : a case report. JDS. 2022;7(1):69–72.
13. Anggraini OD, Komariah C, Prasetyo A. Efek ekstrak kulit mangga arumanis terhadap penurunan edema kaki mencit putih jantan yang diinduksi karagenin. e-Jurnal Pustaka Kesehat. 2018;6(2):267–71.
14. Kunsputri FA, Suhartiningtyas D. Prevalensi stomatitis traumatik pemakai alat ortodonsi lepasan (kajian di rumah sakit gigi dan mulut pendidikan asri medical center Yogyakarta). Insisiva Dent J Maj Kedokt Gigi Insisiva [Internet]. 2013;2(1):57–62. Available from: https://journal.umy.ac.id/index.php/di/article/view/559
15. Tuti Alawiyah. Komplikasi dan risiko yang berhubungan dengan perawatan ortodonti. J Ilm WIDYA [Internet]. 2017;4(1):256–61. Available from: https://e-journal.jurwidyakop3.com/index.php/jurnal-ilmiah/article/view/286
16. Erwansyah E, Fajriani, Ferry AN. Pain perception toward orthodontic treatment. Makassar Dent J. 2020;9(3):177–80.
17. Ramadhani N, Sumiwi SA. Aktivitas antiinflamasi berbagai tanaman diduga berasal dari flavonoid. Farmaka. 2016;14(2):111–23.
18. Sukmawati S, Yuliet Y, Hardani R. Uji aktivitas antiinflamasi ekstrak etanol daun pisang ambon (*Musa paradisiaca L.*) terhadap tikus putih (*Rattus norvegicus L.*) yang diinduksi karagenan. J Farm Galen (Galenika J Pharmacy). 2015;1(2):126–32.
19. Khotimah S, N AM. Riview artikel: beberapa tumbuhan yang mengandung senyawa aktif antiinflamasi. Farmaka. 2017;14(2):28–40.
20. Tiara MS, Muchtaridi M. Aktivitas farmakologi ekstrak daun katuk (*Sauropus androgynus (L.) Merr*). Farmaka. 2018;16(2):398–405.
21. Santoso U. Katuk , Tumbuhan Multi Khasiat [Internet]. 1st ed. Saepudin R, editor. Badan Penerbit Fakultas Pertanian (BPFP) Unib; 2016. 104 p. Available from: https://www.researchgate.net/publication/303994522_Katuk_Tumbuhan_Multi_Khasiat
22. Djamil R, Zaidan S. Isolasi senyawa flavonoid dari ekstrak metanol daun katuk (*Sauropus androgynus (L.) Merr*), euphorbiaceae. J Ilmu Kefarmasian Indones. 2016;14(1):57–61.
23. Setyopuspito Pramitaningastuti A. Uji efektivitas antiinflamasi ekstrak etanol daun srikaya (*Annona Squamosa.*

L.) terhadap edema kaki tikus putih jantan galur wistar. J Ilm Farm. 2017;13(1):8–14.

24. Pramitaningastuti AS, Anggraeny EN. Uji efektivitas antiinflamasi ekstrak etanol daun srikaya (*Annona squamosa. L*) terhadap edema kaki tikus jantan galur wistar. J Ilmah Farm. 2017;13(1):9–14.
25. Ifmaily, Islamiyah, S B, Fitriani, P R. Efek gel daun temu putih (*Curcuma zedoaria (Christm.) Roscoe*) sebagai antiinflamasi dengan metoda induksi karagen dan kantong Granuloma pada mencit putih jantan. J Inov Penelit. 2021;1(3):1–4.
26. Edi Wiranto, Muhamad Agus dan P. Aktivitas antiinflamasi secara in-vitro ekstrak teripang butoh. JKK. 2016;5(1):52–7.
27. Desnita R, Luliana S, Anastasia DS. Antiinflammatory activity patch ethanol extract of leaf katuk (*Sauropus Androgynus L. Merr*). J Ilmu Kefarmasian Indones. 2018;16(1):1–5.
28. Herawati H, Paramayudh F, Satria Darwis R, Syarifah S. Effectiveness of katuk leaves ethanol extract amount of osteoblas and osteoklas on alveolar bone in ortodontic treatment (Research on alveolar bone of guinea pigs). JHDS. 2021;1(1):39–49.
29. Utami ET, Kuncoro RA, Hutami IR. Efek antiinflamasi ekstrak daun sembukan (*Paederia scandens*) pada tikus wistar. Trad Med J. 2011;16(2):95–100.
30. Soleha T, P M. Blueberry (*Vaccinium Corymbosum*) dalam menghambat proses inflamasi. Majority. 2016;5(1):63–7.
31. Nørregaard R, Kwon TH, Frøkiær J. Physiology and pathophysiology of cyclooxygenase-2 and prostaglandin E2 in the kidney. Kidney Res Clin Pract [Internet]. 2015;34(4):194–200. Available from: http://dx.doi.org/10.1016/j.krcp.2015.10.004
32. Prasetya RC. Ekspresi dan peran siklooksigenase-2 dalam berbagai penyakit di rongga mulut. Stomatognatic (JKG Unej). 2015;12(1):16–9.
33. Susanti NMP, Budiman IN., Warditiani NK. Skrining fitokimia ektrak etanol 90 % daun katuk (*Sauropus androgynus L. Merr*.). J Farm Udayana. 2014;3(1):83–6.
34. Andari D, Khan FI, Jakfar SI. Methanol extract of katuk (*Sauropus androgynus*) leaves as an anti-inflammatory agent: animal study in carrageenan-induced rat models of inflammation. MCBS. 2022;6(3):129–34.
35. Nifinluri C, Datu OS, Potalangi N, Pareta D. Uji Aktivitas Anti-inflamasi

Ekstrak Etanol Kulit Buah Pisang Kepok Musa balbisiana Terhadap Kaki Tikus Putih *Rattus novergicus.* Biofarmasetikal Trop. 2019;2(2):15–22.

36. Istiqomah AN, Putra HM, Aligita W, Risa O B. Aktivitas antiobesitas dan antiinflamasi ekstrak etanol daun katuk (*Sauropus androgynus L. Merr*) pada tikus wistar jantan obesitas. J Ilm Ibnu Sina Ilmu Farm dan Kesehat. 2022;7(2):390–400.
37. Mukhtarini. Ekstraksi, pemisahan senyawa, dan identifikasi senyawa aktif. J Kesehatatan [Internet]. 2014;7(2):361–7. Available from: https://doi.org/10.1007/s11293-018-9601-y
38. Wendersteyt NV, Wewengkang DS, Abdullah SS. Uji aktivitas antimikroba dari ekstrak dan fraksi *Ascidian Herdmania momus* dari perairan pulau bangka likupang terhadap pertumbuhan mikroba *Staphylococcus aureus*, *Salmonella typhimurium* dan *Candida albicans*. Pharmacon. 2021;10(1):706–12.
39. Syafitri NE, Bintang M, Falah S. Kandungan fitokimia, total fenol, dan total flavonoid ekstrak buah harendong (*Melastoma affine D. Don*). Curr Biochem. 2014;1(3):105–15.
40. Fathmawati D, Abidin MRP, Roesyadi A. Studi kinetika pembentukan karaginan dari rumput laut. J Tek Pomits. 2014;3(1):27–32.