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Antiinflammatory Activity Patch Ethanol Extract of Leaf Katuk (*Sauropus Androgynus* L. Merr)

(Uji Antiinflamasi *Patch* Ekstrak Etanol Daun Katuk (*Sauropus androgynus* L. Merr))

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Abstract: The leaf katuk (*Sauropus androgynus* L. Merr) extract at a dose of 400 mg/kg BW had antiinflammatory activity in rat by induction of carrageenan. Patch are adhesive plasters containing medicinal substances placed on the skin to delivery active substances. Patch can offer practicality, comfort and accuracy of dosage in the application of leaf *S. androgynus* extract.This research was a laboratory experimental research by making patch of leaf *S. androgynus* extract and inflammation effect used rats as its animal test. Inflammatory healing activity was seen from the percentage reduction in inflammation in rats after patch application. Patch of leaf *S. androgynus* extract dose 400 mg/kg BW has percentage of inflammatory inhibition ranged between 66,67-100%. Statistical test results using one-way anova patch leaf *S. androgynus* extract showed good effectiveness in curing inflammation. Effectiveness between leaf *S. androgynus* extract patch and diclofenac sodium patch relatively the same in curing inflammation.

Keywords: patch, antiinflammatory, leaf *S. androgynus* extract.

Abstrak: Ekstrak daun katuk (*Sauropus androgynus* L. Merr) dengan dosis 400 mg/kg BB memiliki aktivitas antiinflamasi pada tikus dengan induksi karagenan. *Patch* adalah plester perekat yang mengandung bahan obat yang ditempatkan pada kulit untuk mengirim zat aktif. *Patch* menawarkan kepraktisan, kenyamanan dan ketepatan dosis dalam penggunaan ekstrak daun *S. androgynus*. Penelitian ini merupakan penelitian eksperimental laboratorium dengan membuat *patch* ekstrak daun *S. androgynus* dan untuk menguji efek inflamasi/peradangan digunakan tikus sebagai hewan uji. Aktivitas penyembuhan inflamasi terlihat dari persentase pengurangan peradangan pada tikus setelah penggunaan *patch*. *Patch* ekstrak daun *S. androgynus* dengan dosis 400 mg/kg BB memiliki persentase penghambatan peradangan berkisar antara 66,67-100%. Hasil uji statistik menggunakan *one-way* anova, *patch* ekstrak daun *S. androgynus* menunjukkan efektivitas yang baik dalam menyembuhkan peradangan. Efektivitas antara *patch* ekstrak daun *S. androgynus* dan natrium diklofenak relatif sama dalam menyembuhkan peradangan.

Kata kunci: *patch*, antiinflamasi, ekstrak daun *S. androgynus.*

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INTRODUCTION

UTILIZATION of natural resources as an alternative in treatment is very rapidly developed today. One Indonesian native plants used as traditional medicine in inflammatory is leaf katuk (*Sauropus androgynus* L. Merr). Leaf katuk (*S. androgynus*) significantly decrease inflammation in rat with dose 100 mg/kg BW compared with papaverin and morphine. Leaf *S. androgynus* ethanol extract at doses of 400 mg/kg BW had antiinflammatory activity in rat with carrageenan inducers[1]. The leaves of the katuk are also reported to increase milk production in rats[2]. In addition Kustifah, reported that katuk leaf extract production of breast milk without degrading its quality[3]. The leaves of katuk have chemicals such as sterols, resins, tannins, saponins, alkaloids, flavonoids, terpenoids, cardiac glycosides, phenols, and catechols[4]. Phytochemical leaf screening results contain polyphenols, anthocyanins, carotenoids, vitamin C and tannins[5].

Bender and Ismail reported that in 100 g of fresh katuk leaves contained 580 mg of papaverine alkoxide compound[6]. The extract of *S. androgynus* leaf is very potential when given topically it is necessary to develop a delivery system that can offer practicality, comfort and accuracy of dose in the application of leaf extract of *S. androgynus*. The delivery system considered in accordance with the criteria is patch. Patch is adhesive plaster contains medicinal ingredients placed on the skin to deliver the active substance. Patch preparations can be occlusive so as to enhance the hydration and permeability of the skin, thus facilitating the process of absorption of the active substance. By making the extract of *S. androgynus* leaf in the form of patch is expected to increase anti-inflammatory capability and comfort in the use of *S. androgynus* leaf extract.

MATERIAL AND METHODS

MATERIAL. Leaf of katuk (*Sauropus androgynus* L. Merr), aquadest, 96% technical ethanol, acetic acid (CH3COOH) glacial (Merck), concentrated hydrochloric acid (Merck), concentrated sulfuric acid (H2SO4) (Merck), iron (III) chloride (FeCl3) 5% (Merck), chloroform (CH3Cl) (Merck), 0.9% sodium chloride (NaCl), major reagents, molisch reagents, dragendorf reagent, spiritus, Hydroxy Propyl Methyl Cellulose (HPMC Lawsim Zecha), Oppanol B100-polyisobutylene (BASF Indonesia), Methyl Paraben, propylene glycol, glycerin, aquades, 70% ethanol (Ikapharmindo), alcohol swab (Metz), diclofenac sodium (Kimia Farma) and lambda carrageenan (Sigma Aldrich).

METHODS. Simplicia Extraction. Fresh leafy fresh simplicia (*Sauropus androgynus* L. Merr) was extracted with 96% ethanol solvent maceration at room temperature. The extract obtained was evaporated with a vacuum rotary evaporator and keep at 40 °C. The extract was then evaporated above the water bath at 60 °C.

Formulation Gel. The gel preparation formula in this study refers and is the result of the reformulation of the Pandit, V., et al7. Gel leaf *S. androgynous* extract was prepared by dissolving leaf *S. androgynous* extract using aquadest then added ethanol and propylene glycol. The solution was stirred with 1000 rpm stirrers for 15 minutes until completely dissolved. Methyl paraben was dissolved in aquadest then added to gel mass while stirring with strirrer 800 rpm for 5 min. The HPMC is dispersed in water while stirring with a stirrer of 800 rpm for 15 minutes to form a gel mass. The formed gel is allowed to stand for 12 hours until the foam disappears and the gel is clear.

Preparation of Patch (Solvent Casting Technique). The gel mass of 3 grams was poured into a Petri dish with a diameter of 6 cm then dried in a 50 °C oven for 3 hours. After drying, 2.5% polyisobutylene (in n-hexane) solution is poured over 0.8 gram into the formed film. The drying of the dosage was continued in a 50 °C oven for 8 minutes. The formed film is removed from the petri dish and inserted into aluminum foil and sealed plastic container and then stored in the desiccator until it is used.

Evaluation of Patch Weight Uniformity. Picked 3 patches weighed with digital scales. The mean weight and standard deviation are determined.

Patch Thickness Evaluation. The patch thickness was measured by 6 different points of each patch (taken 3 patches randomly) using a digital micrometer and determined the average thickness as well as the standard deviation.

Mechanical Strength Patch. The mechanical strength of the patch is described as tensile strength and% elongation when the film is torn. The mechanical strength of the patch is tested with an autograph consisting of two separately charged parts. The part below is the retained part (not moving), while the upper part is the moving part. Cut films with a certain dimension clipped between two parts, then the style raised gradually until the film is torn.

$$\text{Tensile strength} = \frac{\text{Loads are given when the film layer is torn (kg)}}{\text{Cross sectional area of the film (mm2)}}$$

The percentage of elongation is determined by recording the length before the patch is torn, the

percentage of elongation is determined from the formula below:

$$\% \text{ Elongation} = \frac{\text{Long additions until the film is torn(mm)}}{\text{initial length (mm)}} \times 100\%$$

Evaluation of Moisture Content. The film is weighed individually and stored in a desiccator containing calcium chloride at room temperature for 24 hours. After 24 hours the film should be weighed and determined the percentage of moisture content.

Test Anti-Inflammatory Effects. The test animal is fasted 12 hours before the experiment. Male Wistar rats were divided into 3 groups (each n = 5), the first group was the control group (without drug administration), the second group was given leaf *S. androgynous* extract patch and the third group was given the diclofenac sodium patch. for the transdermal group, patches were applied to the shaved rat skins in the thigh area. The left leg of the mouse is marked with ink on the maleous lateral area. The rat's foot volume was measured using the Pletismometer tool by immersing the rat's foot to the marked extent. Initial volume of rat feet was measured and inflammatory induction was performed with 0.05 mL subcutaneous injection of 2% lambda carrageenan solution in the sub-plantar part of rat's foot[8]. Transdermal drug preparations were administered in group rat two and three, 30 min after induction, while the first group rat as control (not given the drug preparation). Performed rat foot volume measurements at 1, 2, 3, 4, 5, 6, 7 and 8 hours after induced carrageenan lambda.

RESULT AND DISCUSSION

The extraction is done by maseration, soaking the simplicia into the solvent using maseration vessel. The maseration method is chosen because it is safe for compounds that are not resistant to high temperatures, other than that it is easy and uses a simple tool. The results of phytochemical screening of *S. androgynus* extract contain class of phenol, flavonoids, terpenoids and tannins. This result differs from the results of previous studies which suggest that S. androgynus extract contains chemicals such as sterols, resins, tannins, saponins, alkaloids, flavonoids, terpenoids, cardiac glycosides, phenols and catechols[4].

The preparation of leaf *S. androgynus* extract patch is made by first making gel of leaf *S. androgynus* extract. Then the gel is dried to form a film sheet or film layer. The gelling agent used is Hydroxy Propyl Methyl Cellulose (HPMC). HPMC was chosen because it is able to form a flexible film layer and strong. The HPMC concentration used in the patch of leaf katuk extract formula was 9%. This number was selected after an experimental trial using HPMC 8, 9 and 10%. Whereas when using HPMC 8%, the resulting gel is somewhat watered, in contrast to HPMC 9%, the resulting gel is somewhat viscous but easily poured. While the gel produced from 10% HPMC is difficult to pour.

Pouring ability is very important in patch making process. If the gel is too thick and difficult to pour it will be difficult to be formed into a sheet of film. In addition to HPMC in patch of leaf *S. androgynus* extract also uses other additives such as methyl paraben as preservative, propylene glycol and glycerin as plasticizers. Methyl parabens have good activity over a wide pH range at pH 5-8. However, the methyl paraben has a low solubility in water so that it needs a solvent capable of dissolving methyl paraben.

Propylene glycol and glycerin are selected because they can dissolve the methyl paraben well, can be mixed with water, and compatible[9]. Plasticizer used is propylene glycol and glycerin (see table 1). In this research will be seen the influence of plasticizer on the elasticity and strength of the resulting patch. The function of the plasticizer is to fill in the empty space between the polymer molecules so that when hydrated it will connect between the polymers and facilitate the occurrence of diffusion and it can also improve the mechanical properties of the polymer to form a flexible, fragile and fragile polymer layer[10].

Moisture content may indicate physical stability of the preparation. Low moisture content (1.55-3.45%) in the preparation can maintain the physical stability of the patch as it can prevent dryness and patchiness so patches are stable and not fragile but very low moisture content close to zero leads to fragile patches[11]. The patch of leaf S. androgynus extract using propylene glycol as plasticizer has a moisture content of 1.859 ± 0.167% so classified as having good physical stability.

The patch of leaf *S. androgynus* extract that uses glycerin as a plasticizer has a high water content that is vulnerable to microbial contamination which causes the patch to have low physical stability. The optimization result for long drying was obtained that drying for 2 hours resulted in patch with moisture content, tensile strength (TS) and% elongation (EB)

Table 1. Gel formula for leaf *S.androgynus* extract.

Bahan	Formula	
	H1 (% w/w)	H2 (% w/w)
S.androgynus extract HPMC	8	8
Propylene Glykol	9	9
Glycerin	-	1,8 (20% w/w of HPMC)
Mehtyl paraben	1,8 (20% w/w of HPMC)	-
Ethanol	0,20	0,20
Aquadest	40	40
	Ad 100	Ad 100

Table 2 . Weight, thickness, moisture content, tensile strength and% elongation leaf S.androgynus extract patch (n = 3).

Evaluation	Formula	
	H1	H2
Patch Weight (mg)	1,122 ± 0,139	0,586 ± 0,023
Patch thickness (mm)	0,346 ± 0,009	0,269 ± 0,023
(%)Patch moisture content	41,060 ± 7,198	1,859 ± 0,167
Tensile Strength (Kg/mm^2)	0,858 ± 0,162	1,080 ± 0,248
% Elongation	30,564 ± 11,045	62,903 ± 13,183

of the desired patch which has low water content, high tensile strength and high % elongation (see Table 2).

A good patch is a flexible, robust and non-fragile patch that is marked with relatively high TS and EB values, but patches that have too high TS values will be brittle and the folding and pulling process can cause easily torn films for that need additional plasticizer[10]. The addition of plasticizers such as propylene glycol to the polymer will lead to an increase in the elongation, strength and flexibility of the patch, but the addition of plasticizers causes a decrease in tensile strength and Young's modulus[12]. Patches that are soft and weak have low TS and EB values, hard and fragile patches have medium and low EB values, soft and strong patches have medium and high EB values, hard and strong patches have high TS and EB values[13]. The patch of leaf S. androgynus extract using propylene glycol as plasticizer yields tensile strength of 1.080 ± 0.248 kg/mm^2 and a high elongation percent of 62.903 ± 13.183% so that the patch is soft and strong.

While the patch of leaf katuk leaf extract using glycerine as plasticizer resulted in moderate tensile strength of 0.858 ± 0.162 kg/mm^2 and a long elongation length of 30.564 ± 11.045% so the patch is hard and brittle. From the experimental results, the formula which has % elongation close to the library is a patch of leaf *S. androgynus* extract formula using a propylene glycol plasticizer. This suggests the use of propylene glycol as a plasticizer produces a better patch (see Fig. 1 and 2).

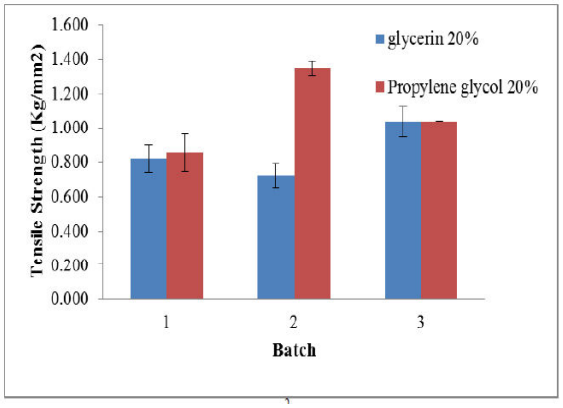

Figure 1. Tensile strength (Kg/mm2) leaf *S. androgynus* extract patch.

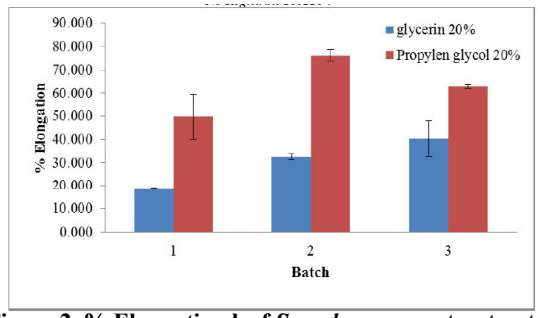

Figure 2. % Elongation leaf *S. androgynus* extract patch

The leaf *S. androgynus* extract patch produced then tested inflammatory healing activity using rat test animals. The inflammatory healing activity test begins with a 0.05 mL injection of a 2% lambda carrageenan solution in rat feet. The test was performed using 3 groups of rat: the first group was the control group (without drugs), group two, transdermal patch of leaf *S. androgynus* extract dose 400 mg/kg BW, the third group was transdermal patch of diclofenac sodium dose 4.5 mg/kg BW. In this anti-inflammatory activity test, it appears that the patch of leaf *S. androgynus* extract has an inflammatory healing effect.

The patch of leaf *S. androgynus* extract dose 400 mg/kg BW and diclofenac sodium dose patch 4.5 mg/kg BW was able to suppress inflammation and differ significantly to control (without drug delivery) at 0,5 to 3 hours with percentage of inflammatory inhibition ranged between 66.67% -100% for patch of leaf *S. androgynus* extract and 44.44% -100% for diclofenac sodium patch, shown in Fig. 3.

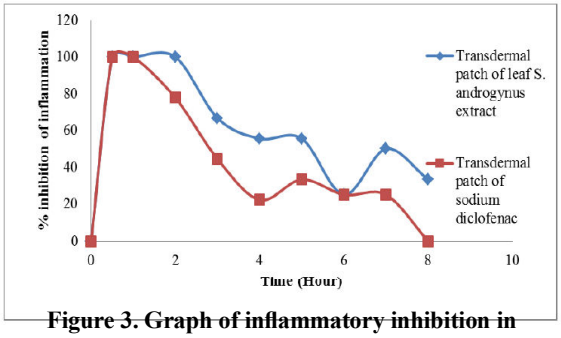

Figure 3. Graph of inflammatory inhibition in transdermal patch of leaf S. androgynus extract (, n=5), transdermal patch group of diclofenac sodium (, n=5)

The statistical test using one way anova test showed that between the AUC the inflammatory percent curve between the control group was significantly different from the transdermal patch of leaf *S. androgynus* extract and the diclofenac sodium patch ($p < 0.05$) so that patch of leaf *S. androgynus* extract showed good effectiveness in curing inflammation. The AUC inflammation curve percentage between the patch of leaf S. androgynus extract did not differ significantly

with the group patch of diclofenac sodium ($p > 0.05$) so that the effectiveness between the leaf *S. androgynus* extract patch and the diclofenac sodium patch were relatively similar in curing inflammation.

CONCLUSION

The leaf *S. androgynus* extract patch using propylene glycol as plasticizer had classified as having good physical stability. The leaf *S. androgynus* extract patch dose 400 mg/kg BW has percentage of inflammatory inhibition ranged between 66,67-100%. Statistical test results using one-way anova patch leaf *S. androgynus* extract showed good effectiveness in curing inflammation. Effectiveness between leaf S. androgynus extract patch and diclofenac sodium patch relatively the same in curing inflammation.

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