Hair Tonic Formulation Containing Ethyl Acetate Fraction of Sweet Potato (*Ipomoea batatas* (L.) Lamk) Leaves and In Vitro Anti-Dandruff Activity Test against Malassezia Furfur

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Abstract. Dandruff is a condition where flaking of the skin occurs excessively on the scalp. The primary cause of dandruff is due to the development of *Malassezia furfur* fungus above normal level. One way to treat dandruff is to reduce the population of *Malassezia furfur* by using herbs that have antifungal activity. This study aimed to prepare a hair tonic containing ethyl acetate fraction of sweet potato leaves and to test antidandruff activity in vitro against Malassezia furfur. Materials and methods: ethyl acetate fraction of 3 % is made hair tonic with the addition of excipient ethanol 96% (5-15%), Propylene glycol (10-30%), tween 80 (1-5%), DMDM Hydantoin, deionized water. Hair tonic was optimized with the d-optimal mixture design method using Design Expert® 10.0.4.0 on physicochemical properties (pH, viscosity, density) and obtained an optimal formula with the use of 96% ethanol of 13.4%, propylene glycol 13.7%, and tween 80 2.9% with a desirability value of 0.881. The optimal formula was tested for antifungal activity against Malassezia furfur using the well-diffusion agar method with PDA-olive oil medium and incubated at 35°C for 3 days. Results showed that hair tonic had strong antifungal activity equivalent to ketoconazole 2%. Conclusion: The ethyl acetate fraction of sweet potato leaves can be formulated into a hair tonic and has strong antidandruff activity.

Keywords: Antifungal, Ethyl Acetate Fraction, Hair Tonic, *Malassezia furfur*, Purple Sweet Potato Leaves.

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1 Introduction

Malassezia furfur is the fungus that causes dandruff and seborrheic dermatitis [1, 2] While genetic influences result in hair that grows thin or baldness occurs [3]. The officially recognized drugs for treating alopecia are minoxidil (topical) and finasteride (oral) [4]. In addition, Ketoconazole (topical) is also used if a fungus causes hair loss and there is no adequate response to treatment with minoxidil and finasteride [5, 6]. Ketoconazole was selected because it is antifungal and has anti-alopecia activity with a mechanism of action similar to finasteride. Alopecia drugs are usually needed for a long time so that long-term side effects can occur, and relapses often occur when drug use is discontinued [4, 7]. Therefore, many people are interested in using natural ingredients as an alternative for the treatment of alopecia.

Natural ingredients widely used in hair care, including preventing hair loss and treating alopecia, are from plants (herbs). One plant that has the potential for hair care is sweet potato (*Ipomoea batatas* (L.) Lamk). Sweet potato is a type of herbaceous plant from the Convolvulaceae family. Commercially, the part of the sweet potato used is the root tuber [8]. Meanwhile, sweet potato leaves are mainly used as animal feed, and a small portion is used as vegetables and medicines [9, 10]. Sweet potato leaves are used by the people of Cameroon as hair cosmetics by grinding, boiling, and macerating them before use [11].

Using sweet potato leaves as hair care cosmetics is caused by their secondary metabolites. The purple sweet potato usually used for treatment is the purple sweet potato. Previous studies have shown that purple sweet potato leaves contain secondary metabolites of steroids, terpenoids, alkaloids, polyphenols, tannins, and flavonoids. In addition, purple sweet potato leaves contain vitamins and minerals [9, 12-15]. The composition and types of secondary metabolites may differ depending on the region where they are grown and depending on the solvent that used to be extracted. The pharmacological activities of sweet potato leaves include antimicrobial, antidiabetic, antioxidant, anti-inflammatory, wound medicine, and dengue hemorrhagic fever medicine [12, 15, 16]. One of the cosmeceutical dosage forms for hair preparations is hair gel. Based on this background, the current study analyzed the secondary metabolite compounds, antifungal activity, and hair growth stimulating activity of purple sweet potato leaves ethanolic extract, fractions, and dosage form of the hair gel.

2 Material and Methods

2.1 Material

Ipomoea batatas leaves were collected from Southeast Sulawesi – Indonesia, in May 2020. Other materials used in these experiments are *Malassezia furfur*, Potato Dextrose Agar – 1% olive oil (PDA-oil), ethanol, n-hexane, ethyl acetate, butanol, aqua distillate, Carbopol 940, propylene glycol, triethanolamine, DMDM hydantoin, phenoxyethanol, deionized water, sodium carboxymethyl cellulose (Sodium CMC), minoxidil,

ketoconazole, reagents for phytochemical screening. The animal test that is used is local male rabbits.

2.2 Extraction

The leaves powder (500g) was macerated in 4000 ml of 96% ethanol. The solvent was changed daily for three days. The macerate was then collected and concentrated using a rotary evaporator (Buchi R-100) at 50°C until viscous ethanolic extract was obtained.

2.3 Fractionation

The ethanolic extract was fractionated in steps by dissolving in hot aqua distillate and then fractionated successively with n-hexane solvents, ethylene acetate, and butanol until n-hexane, ethyl acetate, butanol, and aqueous fractions were obtained. The extract and its fractions were stored in a refrigerator till further analysis.

2.4 Phytochemical Screening

The extract and its fractions were tested for secondary metabolites using a reagent test according to the Farnsworth method [17] and the TLC (thin layer chromatography) method. TLC was performed on Kieselgel 60 F254 (Merck®), spots were viewed under UV light at 254 and 356 nm, then sprayed with 10% H_2SO_4 and a specific reagent, and then heated on a hot plate.

2.5 Gas Chromatography-Mass Spectrometry (Gc-Ms) Analysis

An instrument from Thermo Scientific conducted a GC-MS analysis of the extract and its fractions. The compounds were identified by matching the similarity of mass spectral data with the data library from Chromeleon software.

2.6 Preparation of Hair Gel Formulation

The hair gel was prepared by dispersing carbopol 940 into deionized water for 24 hours and homogenized. Next, triethanolamine was added to the carbopol dispersion, then mixed homogeneously to obtain a gel base. Propylene glycol, ethyl acetate fraction, and other ingredients were poured and mixed homogeneously with a gel base until a hair gel was formed [18]. The composition of hair gel is shown in Table 1.

Table 1. Composition of hair gel containing ethyl acetate fraction of purple sweet potato leaf.

No.	Compound	Concentration (%)
1	Ethyl acetate fraction	3
2	Carbopol 940	2
3	Propylene Glycol	25,5

4	Triethanolamine	2,5
5	DMDM Hydantoin	0,2
6	Phenoxyethanol	1
7	Deionized water	Ad 100%

2.7 Evaluation of Organoleptic Properties

Hair gel was visually inspected for organoleptic parameters of color, odor, and homogeneity [18].

2.8 pH Measurement

The pH of the hair gel was measured using a digital pH meter. Before use, the pH meter was calibrated using standard pH 4 and pH 7 buffer solutions [18].

2.9 Viscosity

The viscosity of the hair gel was measured with a Rhion viscometer. Viscosity measurement was conducted by placing the sample in a viscometer until the spindle was submerged. The spindle was set at a speed of 50 rpm [19].

2.10 Spreadability

About 0.5 g of hair gel was placed within a round glass plate over which a second round glass plate was placed. A weight of 100 g was placed on the upper round glass plate. The diameter of the spreading hair gel due to the placement of weights was recorded [18].

2.11 Antifungal Activity

The fungi *Malassezia furfur* were obtained from Indonesia University, Jakarta. The fungi were maintained in potato dextrose agar-olive oil (PDA-oil). For three days, the fungal culture was grown in PDA oil at 35°C. The fungal culture suspension was adjusted to visually comparable turbidity of 0.5 scales MacFarland standard equal to 1.5 x 10^9 CFU/ml. The antifungal activity of the extract and its fractions were performed by the agar diffusion method [20]. Briefly, the PDA oil was prepared and taken in sterile Petri plates. The fungal suspension was spread uniformly on the surface of PDA oil. 20µl suspension of the sample test was added in an empty sterile well with various concentrations. Sodium CMC suspension was used as a negative control, and ketoconazole suspension was used as a positive control. For three days, the plates were incubated at 35°C to find the fungistatic effect. Three replicate plates were used for treatment.

3 Results and Discussion

Ipomoea batatas have been traditionally used for hair care. One of the hair care problems is hair loss or alopecia. The causes of alopecia range from genetic to environmental. Based on this traditional claim, phytochemical screening is conducted to determine its phytochemical compounds and tested for its antifungal and hair growth stimulant activity.

3.1 Phytochemical Analysis

There are different results between the preliminary test and the GC-MS test. GC-MS analysis showed that the ethanolic extract contains secondary metabolites such as alkaloids (N-propyl-2-hydroxy-1-oxohexahydro-1H-azepine; pyroglutamic acid; 3',8,8'-trimethoxy-3-piperydil-2,2'-binaphtalene-1,1',4,4'-tetrone; 1,8-diazacylclotetradecane-2,9-dione), steroids (estra-1,3,5 (10)-trien-17β-ol; propanoic acid, 2-(3-acetoxy-4,4,14-trimethylandrost-8-en-17-yl-), terpenoids (α-cadinol; isoaromadendrene epoxide; -(-) spathulenol), aldehydes, and fatty acids (Table 2). Meanwhile, the preliminary screening tests alkaloids, steroids/terpenoids, flavonoids, tannins, and polyphenols (Table 3). Similar results are shown by all those fractions of sweet potato leaves.

These results indicated that GC-MS identified not all of the compounds in the preliminary test. The compounds detected using GC-MS only the compounds can be volatile, so a secondary metabolite was detected in the preliminary test but not in the GC-MS analysis.

Table 2. Phytochemical compounds in ethyl acetate fraction by GC-MS.

No.	Compound name	Mol. Weight (g/mol)	Mol. Formula	Retention time (RT) (min)
1	2H-Pyran-2-one, tetrahydro-6,6-dimethyl-	128	$C_7H_{12}O_2$	4.14
2	1-Propanamine, N,2-dimethyl-N-nitroso-	116	$C_5H_{12}N_2O$	5.15
3	2,2-Dimethyl-3-hydroxypropionaldehyde	102	$C_5H_{10}O_2$	6.23
4	Bicyclo[3.1.0]hexan-3-one	96	C_6H_8O	6.90
5	Cyclobutane, methylene-	68	C_5H_8	7.37
6	Cyclohexanone, 3-hydroxy-	114	$C_6H_{10}O_2$	8.50
7	Propenal dimethylhydrazone	98	$C_5H_{10}N_2$	8.71
8	4,4-Ethylenedioxy-pentanenitrile	141	$C_7H_{11}NO_2$	9.81
9	1H-Pyrrole, 2,5-dihydro-1-nitroso-	98	$C_4H_6N_2O$	10.17
10	2-Cyclopropylcarbonyloxydodecane	254	$C_{16}H_{30}O_2$	10.43
11	1-Butanamine, N-methyl-N-nitroso-	116	$C_5H_{12}N_2O$	10.65
12	2-Butoxyethyl acetate	160	$C_8H_{16}O_3$	11.47

13	Tetrahydropyrrole-3-amino-2,5-dione	114	$C_4H_6N_2O_2$	12.22
14	Heptane, 1-nitro-	145	$C_7H_{15}NO_2$	13.18
15	3,6-Octadecadiynoic acid, methyl ester	290	$C_{19}H_{30}O_2$	13.63
16	S-[2-Aminoethyl]-dl-cysteine	164	$C_5H_{12}N_2O_2S$	16.79
17	dl-Allo-cystathionine	222	$C_7H_{14}N_2O_4S$	17.13
18	Imidazole, 2-amino-5-[(2-carboxy)vinyl]-	153	$C_6H_7N_3O_2$	17.75
19	4-Cyclopropylcarbonyloxytridecane	268	$C_{17}H_{32}O_2$	18.03
20	9-Oxabicyclo[6.1.0]nonan-4-one	140	$C_8H_{12}O_2$	19.77
21	1-Decanol, 2-ethyl-	186	$C_{12}H_{26}O$	19.97
22	Pyrrolidine, 1-nitro-	116	$C_4H_8N_2O_2$	20.91
23	Tetracyclo[3.3.0.0(2,4).0(3,6)]oct-7-ene-4-carboxylic acid, methyl ester	162	$C_{10}H_{10}O_2$	21.36
24	5-Nonanol, 5-methyl-	158	$C_{10}H_{22}O$	21.83
25	3-(Prop-2-enoyloxy)dodecane	240	$C_{15}H_{28}O_2$	22.47
26	Ethenyl tert-butyl sulfoxide	132	$C_6H_{12}OS$	23.03
27	Mannosamine	179	$C_6H_{13}NO_5$	24.22
28	E-2-Tetradecen-1-ol	212	$C_{14}H_{28}O$	24.67
29	3-Cyclopropylcarbonyloxytetradecane	282	$C_{18}H_{34}O_2$	24.75
30	1-Heptanol, 2-propyl-	158	$C_{10}H_{22}O$	24.84
31	3-Trifluoroacetoxydodecane	282	$C_{14}H_{25}F_3O_2$	27.41
32	3-Cyclopropylcarbonyloxytridecane	268	$C_{17}H_{32}O_2$	27.67
33	Z,Z-2,5-Pentadecadien-1-ol	224	$C_{15}H_{28}O$	30.57
34	E-7-Tetradecenol	212	$C_{14}H_{28}O$	30.93
35	2-Cyclopropylcarbonyloxytridecane	268	$C_{17}H_{32}O_2$	31.15
36	Octanoic acid, 2-methyl-	158	$C_9H_{18}O_2$	31.82
37	3-Trifluoroacetoxypentadecane	324	$C_{17}H_{31}F_3O_2$	32.13
38	2-(Prop-2-enoyloxy)pentadecane	282	$C_{18}H_{34}O_2$	32.27
39	trans-3,4-Epoxynonane	142	$C_9H_{18}O$	32.67
40	1-(Hydroxymethyl)-1-(2'-hydroxyethyl) cyclopropane	116	$C_6H_{12}O_2$	33.13
41	9-Oxabicyclo[6.1.0]nonan-4-ol	142	$C_8H_{14}O_2$	33.97
42	2H-Pyran, 2,2'-[1,10-decanediylbis(oxy)]bis[tetrahydro-	342	$C_{20}H_{38}O_4$	34.50
43	Cycloheptanol, 2-chloro-, trans-	148	$C_7H_{13}ClO$	35.13
44	Cyclopentaneundecanoic acid, methyl ester	268	$C_{17}H_{32}O_2$	35.60
45	Oxetane, 2-methyl-4-propyl-	114	$C_7H_{14}O$	36.34
46	9-Tetradecen-1-ol, acetate, (E)-	254	$C_{16}H_{30}O_2$	37.23
47	2-Trifluoroacetoxydodecane	282	$C_{14}H_{25}F_3O_2$	42.13
48	Sulfurous acid, butyl octyl ester	250	$C_{12}H_{26}O_3S$	43.18
49	3-(Prop-2-enoyloxy)tetradecane	268	$C_{17}H_{32}O_2$	48.73

Table 3. Preliminary phytochemical test.

No.	Test	Extract/Fraction				
		ethanol	n-hexane	ethyl acetate	butanol	aqueous
1	Alkaloids	+	-	-	+	-
2	Polyphenols	+	+	+	+	+
3	Tannins	+	-	+	+	+
4	Saponins	-	-	-	-	+
5	Flavonoids	+	+	+	+	-
6	Steroids/terpenoids	+	+	+	+	-
7	Glycosides	-	-	+	-	-

3.2 Evaluation of the Organoleptic Properties of Hair Tonic

We selected ethyl acetate fraction to formulate as hair gel because this fraction showed to have both abilities, i.e. as an antifungal and as a hair growth stimulation with highest activity. Evaluation studies showed that hair gel has the desired organoleptic properties of consistency, color, odor, homogeneity, pH, and viscosity for topical preparations. The results of an evaluation of hair gel are shown in Table 4. Formulation studies were only carried out on organoleptic properties so that for further development still requires further investigations. Hair gel of ethyl acetate fraction is seen in Fig. 1.

Fig. 1. Hair gel of ethyl acetate fraction.

Table 4. Evaluation of organoleptic properties of hair gel.

No.	Test	Result
1	Consistency	Semisolid
2	Odor	Typical
3	Color	Blackish brown
4	pH	6.08
5	Viscosity	250 dPas
6	Spreadability	5.2 cm

3.3 Antifungal Activity

The in-vitro antifungal assay of the extract demonstrated activity against *Malassezia furfur* depending on doses. There is no activity at a 5% ethanolic extract, and activity starts at a concentration of 10% with weak activity. The antifungal activity increased with the increase in the extract concentration (Fig. 2, Table 5). The fractions showed that all had activity against *Malassezia furfur* where strong activity was found in aqueous and ethyl acetate fractions while n-hexane and butanol fractions had weak antifungal activity (Fig. 2, Table 6). Hair gel showed that the gel bases didn't block the activity of the fraction in inhibiting the growth of fungi (Fig. 2, Table 7). This study is only a preliminary test, so further investigation is necessary. Secondary metabolite compounds thought to have an antifungal effect are alkaloids, terpenoids, flavonoids, tannins, and polyphenols.

Table 5. Inhibition zone of the ethanolic extract against *Malassezia furfur*.

Sample	Diameter inhibition zone (mm) (mean ± Standard deviation; n=3)	Interpretation
Positive control (ketoconazole)	25.3±2.2	Susceptible
Negative control (sodium CMC)	-	-
5% ethanolic extract	-	-
10% ethanolic extract	8.2±0.3	Resistant
20% ethanolic extract	10.6±2.3	Resistant
40% ethanolic extract	20.2±2.5	Intermediate
80% ethanolic extract	23.6±2.4	Susceptible

Table 6. Inhibition zone of fractions against *Malassezia furfur*.

Sample	Diameter inhibition zone (mm) (mean ± Standard deviation; n=3)	Interpretation
Positive control (ketoconazole)	28.6±0.4	Susceptible
Negative control (sodium CMC)	-	
n-hexane fraction	11.0±0.3	Resistant
Ethyl acetate fraction	39.9±2.5	Susceptible
Butanol fraction	11.5±0.3	Resistant
Aqueous fraction	30.8±0.4	Susceptible

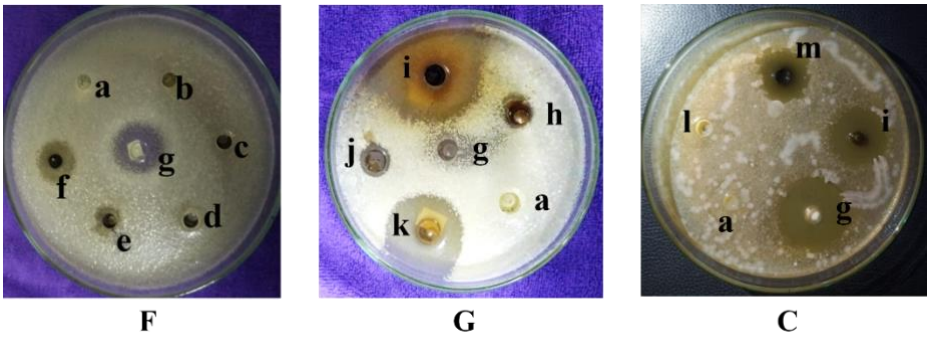

Fig. 2. Antifungal activity of purple sweet potato leaves against *Malassezia furfur*.

Table 7. Inhibition zone of hair gel against *Malassezia furfur*.

Sample	Diameter inhibition zone (mm) (mean ± Standard deviation; n=3)	Interpretation
Positive control (ketoconazole)	29.9±0.2	Susceptible
Negative control (sodium CMC)	-	
Hair gel bases	-	
Ethyl acetate fraction	24.83±0.5	Susceptible
Hair gel	21.85±1.1	Susceptible

The mechanism of alkaloids as antifungals is to damage the fungal cell membrane. Alkaloids bind to ergosterol to form holes that cause cell membrane leakage. Membrane leakage causes fungal cell damage and then fungal cell death [21]. Tannins act by binding to the cell membrane structure of the fungal similarly [22]. Tannins have an affinity for ergosterol and polyphenols. Tannins' binding to fungal membranes is possibly in antifungal action [23]. Both hydrolyzed and condensed tannins have antifungal activity. Phenolics or polyphenols have a benzene ring with one or more hydroxyl groups; a hydroxyl group on the benzene ring increases the toxicity of these compounds [24]. Polyphenols are essential for plants and contribute resistance to microorganisms, herbivores, and insects [25]. There are several mechanism actions of phenolics to counteract pathogenic microbial have been suggested, including through disruption of enzymatic processes. This process involves energy production and synthesis of structural components by weakening and destroying the cell membrane's permeability barrier by altering the cells' physiological status or affecting nucleic acid synthesis [26]. The mode of action of antimicrobial flavonoids may be through several targets. One is to form complexes with proteins by nonspecific bonds, including hydrogen bonds and hydrophobic effects, and through forming covalent bonds. So, the mechanism of antimicrobial action may be associated with their ability to activate attachment to microbes, cell envelope transport proteins, enzymes, and others. Lipophilic flavonoids may also interfere with the membranes of microbes [27, 28]. Terpenoids have antifungal activity in various ways, such as interfering with cell wall

permeability, binding to ergosterol to interfere with cell membrane permeability, and inhibiting the formation of pseudohyphae, and chlamydoconidia [29].

Based on GC-MS analysis data, ethanolic extract compounds that have antifungal activity are 1-isopropyl-4,7-dimethyl-1,2,3,5,6,8a-hexahydronaphthalene; α-cadinol [30]; isoaromadendren epoxide [31]; ethyl isoallocholate [32]; 3',8,8'-trimethoxy-3-piperidyl-2,2'-binaphthalene-1,1',4,4'-tetrone; propanoic acid; 2-(3-acetoxy-4,4,14-trimethylandrost-8-en-17-yl)- [32]. The ethyl acetate fraction that has antifungal activity is 1H-Pyrrole, 2,5-dihydro-1-nitroso- [33], dl-Allo-cystathionine [34], Imidazole, 2-amino-5-[(2-carboxy)vinyl]- [35], Octanoic acid, 2-methyl- [36], Pyrrolidine, 1-nitro-, Tetrahydropyrrole-3-amino-2,5-dione [37]. Water fraction that have antifungal activity are 1H-Pyrrole, 2,5-dihydro-1-nitroso- [33], Carbonic acid, bis(1-methylethyl) ester [38], dl-Allo-cystathionine [34], Imidazole, 2-amino-5-[(2-carboxy)vinyl]- [35], Pyrazole-4-carboxaldehyde, 1-methyl- [39].

4 Conclusion

This research showed the potential of ethanolic extract, its fractions, and its hair gel formulation from purple sweet potato leaves as anti-alopecia through hair growth activity on rabbit males and antifungal activity through inhibited *Malassezia furfur* growth. The activity of the ethanolic extract and its fractions is due to the secondary metabolite compounds. Ethanolic extract, aqueous fraction, and ethyl acetate fraction can be used to develop plant medicines against *Malassezia furfur*. Ethanolic extract and its fraction can be used as an alternative treatment for stimulating hair growth because its activity is essential in preventing hair loss. The ethyl acetate fraction of purple sweet potato leaves can be made in the topical dosage form as hair gel that has anti-alopecia activity, both as an antifungal and as a hair growth stimulation.

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Conflict of Interest

The authors declare there's no conflict of interest

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