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Identification of Metabolite Compounds and Biological Activity of *Diplazium esculentum*

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Abstract: *Diplazium esculentum is one of the medicinal plants used by Dayak tribes in Central Kalimantan to cure acne. The potential of D. esculentum can be proved through information on the active compounds of the extract obtained in decoction and infusa methods. Thus, a liquid chromatography-mass spectrophotometry (LC-MS)-based method is developed to identify the active compounds of D. esculentum extract in either decoction method or infusa method. The chemical compound potential of D. esculentum extract was then analysed using bioinformatics approach based upon the database of PASS online server. Results showed that the D. esculentum extract contained 81 chemical compounds in decoction method and 68 compounds in infusa method, in which the dominant compound was flavonoid. Moreover, PASS online web server analysis found 7 flavonoid compound groups potential as anti-acne containing antisebor, AR expression inhibitor and CYP1A1 inhibitor. This information could be very useful for designing a clinical test on plant natural compound potential for traditional drug development.*

Keywords: *Medicinal plant, Fern, Anti-acne, Decoction and Infusa methods.*

Introduction

Vegetable fern *Diplazium esculentum* is a plant wildly growing in the river bank and highly humid garden. This plant is one of the medicinal plants used by Dayak tribe in Central Kalimantan to traditionally cure acne [35]. The ferns used as medicine can become source of good natural bioactive product that is potentially developed as new drug [4].

There are 4 factors affecting the occurrence of acne, epidermic follicular hyper-proliferation, increased sebum production, inflammation, and growth of *Propionibacterium acnes* production and follicular hyperkeratosis gives favourable pilobaceous condition for *P. acnes* growth [5].

Phytochemical screening of *D. esculentum* indicates the presence of polyphenol, alkaloid, tanin and saponin through ethanol extraction and flavonoid, polyphenol, alkaloid, tanin, and saponin in water extraction [36]. Flavonoid is only found in water extraction, decoction method and infusa method, but few information is available for active compounds of *D. esculentum* in water extract of both methods. To obtain information on chemical compounds of *D. esculentum* water extract, liquid chromatography-mass spectrometry

(LC-MS) is used, since this analysis can yield large spectral data [25]. This technique possesses specificity and very high sensitivity.

The use of water extraction is environmental friendly because the plant is not victimized and the organic solvent is substituted with easy, economic, sound, and safe alternative [31] compared with other chemical solvent, such as ethanol. Solvent determination and temperature can influence the extract quantity and quality of plant and its bioactive compounds [14].

Previous studies found the presence of relationship between flavonoid structure and its antibacterial activity [6]. Kaempferol as derivative of flavonoid in *Zingiber spectabile* Griff has antioxidant activity [26]. Luteolin, quercetin, and resveratrol also show antibacterial activity against *Staphylococcus aureus* [27]. Therefore, the potential of a medicinal plant is influenced by its chemical compounds and chemical structures.

This study aims to identify the active compounds of *D. esculentum* as herbal drug for acne treatment using LC-MS and determine the biological activity. The potential of *D. esculentum* as herbal medicine is recently unclear and has become major challenge to scientific approach, through *in vitro* and *in vivo* studies.

Materials and methods

Diplazium esculentum was collected from Palangkaraya, Central Kalimantan, Indonesia. Water was employed as solvent. Samples were cleansed and dried for about 5 days, finely ground, and extracted in distilled water using decoction method and infusa method. The former was carried out by putting one-hundred g of *D. esculentum* in 1000 mL of aquadest and boiled up to 90 °C, then filtered. The latter was done by pouring one-thousand ml of aquadest into a pan and boiled up to 90 °C, turned off the fire and added with 100 g of *D. esculentum* for 30 minutes, then filtered.

LC-MS analysis

Metabolite compound identification used Shimatsu LC-MS-8040 LC/MS. One µL of sample was injected into Shim Pack FC-ODS (2 mm D × 150 mm, 3 µL) column with a capillary voltage of 3.0 kV and column temperature of 35 °C. The LC-MS analysis employed UPLC-MS equipped with binary pump. LC is connected to QTOF mass spectrometer joined with ESI. MS utilized positive ionization mode. The ESI parameter was set at the source temperature of 100 °C, 0.6 seconds scanning, and 80 minutes run time.

Biological activity analysis

A biological activity study is a basis required to set or select new molecule. The compound biological activity analysis utilized PASS online server [20]. It analyses the drug, biological activity, and various chemical compound targeting interactions. This server provides tools to select the compound of determined biological activity profiles including the pharmacotherapic effect desired and biochemical mechanism predicted as input information and provides electronic report on chemical compound literature. Biological potential analysis of compounds was carried out by inputting the chemical structures of *D. esculentum* extract obtained from LC-MS analysis in MOL file format or SDFile format on PASS online server. The outcome will show the biological potential of the compound based upon the database and accomplished with probability activity (PA) value, in which PA value ≥ 0.7 indicates that the computing prediction is not much different from the clinical test, while PA value ≤ 0.3 reflects that there is 50% probability similarity of the computing prediction to the clinical test. In the present study,

PASS online server analysis was directed to the compound potential of *D. esculentum* extract as antiseborrheic, AR expression inhibitor, and CYP1A1 inhibitor with PA ≥ 0.7.

Results and discussion

This study found that the water extraction of *D. esculentum* containes various compounds as presented in Table 1.

Table 1. Number of metabolite compounds in water extraction of *D. esculentum* (decoction and infusa methods)

Method	Number of metabolite compounds
Decoction	81 compounds
Infusa	68 compounds

Table 1 demonstrates that the water extraction of *D. esculentum* in decoction method and infusa method contains various metabolite compounds – flavonoid, saponin, terpenoid, and carboxylic acid groups. *D. esculentum* extract holds more metabolite compounds in decoction method, 81 compounds, than those in infusa method, 68 compounds. This study found that water solvent is effective to use as organic solvent since it can filter various active compounds of *D. esculentum* extract, and difference in number of compounds indicates that decoction method is more effective than infusa method in water extraction. It could result from that compound solubility will rise with increasing temperature [3], boiling duration needs to be considered since increased boiling time in decoction method could result in decline in number of compounds in the extract [9].

The present study showed that dominant active compound of *D. esculentum* was flavonoid. Polyphenolic compounds produced by the plant and sent to human body through food and its occurrence in the tissue is dependent upon the intake of plant product [29]. Flavonoid has ability to induce human protecting enzyme system [17], such as anti-oxidant, anti-inflammation, anticancer, and cardiovascular protection [32]. Flavonoid extracted from *Cystoseira compressa* holds antibacterial activity as well [1], depending upon the structure, the substitution on the aromatic ring [33].

Water extraction of *D. esculentum* yields 31 flavonoid compound groups in decoction method (Table 2) and 24 compounds in infusa method (Table 3). There are more compounds of flavonoid group in decoction method than that in infusa method, since decoction method supports extraction better than infusa method and more appropriate for heat-resistant compounds, hard plant material, such as root, and will yield more soluble in oil than that in infusa method [2].

Table 2 shows that decoction method-based water extraction of *D. esculentum* contains 31 flavonoid compounds with the highest composition of calycosin 7 O ß D glucoside and naringenin, 2.14473% and 2.01286%, respectively, and the lowest composition is procyanidin, 0.25975%. Naringenin has potential as antibacterial agent, especially against *Staphylococcus aureus* [19].

Table 3 demonstrates that infusa method-based water extraction of *D. esculentum* contains 24 flavonoid compounds with the highest composition of calycosin 7 O ß D glucoside and naringenin, 2.134107% and 2.002882%, respectively, the lowest composition is recorded in

6 α hydroxymedicarpin, 0.423520%. More dominant flavonoid compound in water extraction of *D. esculentum* of both methods could result from high solubility of flavonoid in water, especially flavonoid glycoside [8].

Table 2. Metabolite compounds of flavonoid group in decoction method-based water extraction of *D. esculentum* (31 flavonoid compounds)

No	Compound	Molecular weight	Composition, %
1	Daidzein	254.24	0.40116
2	Coumestrol	268.22	0.95406
3	Biochanin B	268.26	1.62682
4	Apigenin	270.24	1.13494
5	Genistein	270.24	0.46703
6	Naringenin	272.25	2.01286
7	9 O methylcoumestrol	282.25	0.96241
8	Biochanin A	284.26	1.62318
9	Calycosin	284.26	1.13049
10	Homopterocarpin	284.31	1.02081
11	Luteolin	286.24	1.62337
12	6 a hydroxymedicarpin	286.28	0.42561
13	Quercetin	302.24	1.62634
14	Kaempferol 3 sulphate	365.29	1.10372
15	Daidzin	416.38	0.92221
16	Genistin	432.38	1.08384
17	Kaempferol 3 rhamnoside	434.35	0.98005
18	Calycosin 7 O ß D glucoside	446.40	2.14473
19	Kaempferol 3 glucoside	448.38	1.49673
20	Kaempferol 7 O ß D glucopyranoside	448.38	0.86479
21	Luteolin 7 glucoside	448.38	1.38711
22	Isoquercitrin	464.38	1.56773
23	Hyperoside	464.38	1.54309
24	Querciturone	478.36	0.85962
25	Leucocyanidin	306.27	0.78915
26	Luteolinidin 5 glucoside	432.38	0.37113
27	6” O malonylgenistein	518.42	0.27540
28	Biochanin A 7 O β D glucoside 6” O malonate	532.45	1.65780
29	Naringin	580.53	1.71495
30	Procyanidin	594.52	0.25975
31	Rutin	610.52	1.38667

Metabolite compounds of *D. esculentum* extract using either decoction method or infusa method could become very useful information for scientific prove in relation with the potentials as medicine. *D. esculentum* is one of the medicinal plants used by Dayak tribe in Central Kalimantan to traditionally cure acne [36]. It is important for traditional drug development from plant extract through ethnomedicinal usage history [15, 28].

Based on the results of previous studies, *D. esculentum* has several potentials. *D. esculentum*, a commonly consumed seasonal vegetable, has been reported to have some pathological

effects, especially on the male reproductive function. The study result show that *D. esculentum* has a potential as an antifertility agent after trial of male Swiss albino mouse [24]. Besides that, *D. esculentum* also potential as anti-coagulant agent [21] and as antioxidant and antidiabetic agent [13].

Table 3. Metabolite compounds of flavonoid in infusa method-based water extraction of *D. esculentum* (24 flavonoid compounds)

No	Compound	Molecule weight	Composition, %
1	Daidzein	254.24	0.658690
2	Coumestrol	268.22	0.949400
3	Biochanin B	268.26	1.618841
4	Apigenin	270.24	1.129313
5	Genistein	270.24	0.464718
6	Naringenin	272.25	2.002882
7	9 O methylcoumestrol	282.25	0.957634
8	Biochanin A	284.26	1.615133
9	Calycosin	284.26	1.124871
10	Homopterocarpin	284.31	1.015743
11	Luteolin	286.24	1.615322
12	6 a hydroxymedicarpin	286.28	0.423520
13	Quercetin	302.24	1.618282
14	Kaempferol 3 sulphate	365.29	1.098278
15	Daidzin	416.38	0.917642
16	Genistin	432.38	1.078467
17	Kaempferol 3 rhamnoside	434.35	0.975201
18	Calycosin 7 O ß D glucoside	446.40	2.134107
19	Kaempferol 3 glucoside	448.38	1.489309
20	Kaempferol 7 O ß D glucopyranoside	448.38	0.860512
21	Luteolin 7 glucoside	448.38	1.380228
22	Isoquercitrin	464.38	1.559954
23	Hyperoside	464.38	1.535424
24	Querciturone	478.36	0.855362

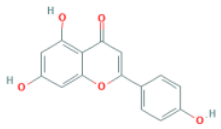
Based on PASS online server analysis, there are 7 compounds of flavonoid groups' potential to cure the acne (Table 4). Especially the compounds of flavonoid groups contained in water extraction of *D. esculentum*.

Table 4 shows that there are 7 of 13 flavonoid groups potential as antiacne based upon the database of PASS online server indicated with anti-seborrheic, AR expression inhibitor and CYP1A1 inhibitor. The compounds are apigenin, genistein, daidzein, biochanin A, biochanin B, calycosin and quercetin, as antiseborrheic, AR expression inhibitor, and CYP1A1 inhibitor, with PA $\geq$ 0.7. Previous study has shown that apigenin inhibits inflammatory response caused by *P. acnes* [10]. *P. acnes* has lypolitic ability since lipase enzyme can hydrolyze fat to fatty acid and glycerol. Skin tissue of sebaceous gland hyperkeratinizes, blocks the pores, and develops the pustules [30]. Other potential compounds are genistein and daidzein clinically examined to be able to treat inflammation from acne [18, 23, 34]. Quercetin through *in vitro* test also has activity to fight against bacteria *P. acnes* [16].

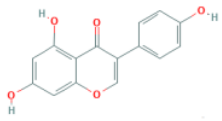
Table 4. Biological activity of *D. esculentum* flavonoid based on PASS online server analysis

No	Compounds	Probability activity (PA)		
		Anti seborrheic	AR expression inhibitor	CYP1A1 inhibitor
1	Apigenin	0.806	0.773	0.745
2	Genistein	0.832	0.872	0.850
3	Daidzein	0.835	0.831	0.756
4	Naringenin	0.811	-	0.894
5	9 0 methylcoumestrol	0.780	0.833	-
6	Biochanin A	0.803	0.869	0.947
7	Biochanin B	0.807	0.828	0.892
8	Calycosin	0.720	0.871	0.930
9	Coumestrol	0.813	0.836	-
10	Hyperoside	-	0.554	0.323
11	Leucocyanidin	0.794	-	-
12	Luteolin	0.873	0.859	-
13	Quercetin	0.835	0.894	0.916

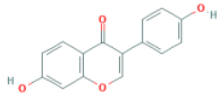
Furthermore, there are 12 potential compounds only as anti-seborrheic, to reduce excessive sebum release of the tissue. Seborrheic is a chronic inflammatory skin disturbance in puberty, from increased skin lipid produced by sebaceous gland development promoting sebum secretion [12]. Those are apigenin, genistein, daidzein, naringenin, 9 0 methylcoumestrol, biochanin A, biochanin B, calycosin, coumestrol, leucocyanidin, luteolin and quercetin (Fig. 1).



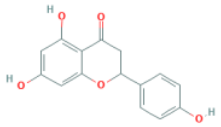
Apigenin (a)



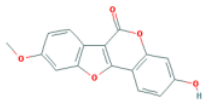
Genistein (b)



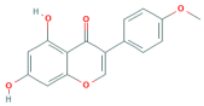
Daidzein (c)



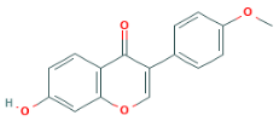
Naringenin (d)



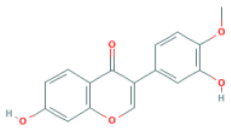
9-O-Methylcoumestrol (e)



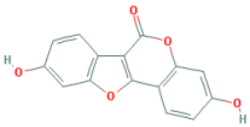
Biochanin A (f)



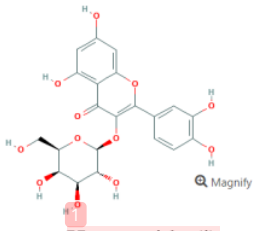
Biochanin B (g)



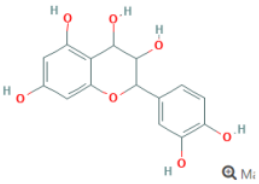
Calycosin (h)



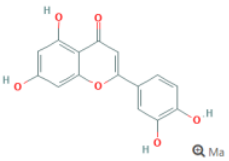
Coumestrol (i)



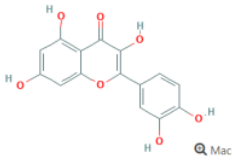
Hyperoside (j)



Leucocyanidin (k)



Luteolin (l)



Quercetin (m)

Fig. 1 Flavonoid major class structure: apigenin (a), genistein (b), daidzein (c), naringenin (d), 9 0 methylcoumestrol (e), biochanin A (f), biochanin B (g), calycosin (h), coumestrol (i), hyperoside (j), leucocyanidin (k), luteolin (l), and quercetin (m) [22].

Table 3 also shows that there are 10 of 13 flavonoid groups' potential as anti-acne in androgen receptor expression inhibitor indicator. Inhibition of androgen receptor can control the appearance of acne [11]. Ten potential compounds as androgen receptor expression inhibitor in *D. esculentum* extract are apigenin, genistein, daidzein, 9 0 methylcoumestrol, biochanin A, biochanin B, calycosin, coumestrol, luteolin and quercetin. Furthermore, there are also 8 of 13 flavonoid compounds of *D. esculentum* extract potential as anti-acne in CYP1A1 inhibitor indicator. CYP1A1 expression in human skin is a key marker of aryl hydrocarbon receptor (AHR) activation that causes the presence of blackheads [7]. Those are apigenin, genistein, daidzein, naringenin, biochanin A, biochanin B, calycosin and quercetin.

Conclusion

Diplazium esculentum extract containes various active compounds that are potential to be developed as new drug for acne treatment. This result also reflects that water could be used as more economic and safe alternative solvent. Different number of compounds obtained in both extraction methods has indicated higher effectivity of decoction method than infusa method. In addition, this study could become early step of traditional medicine development using natural material and method.

Acknowledgments

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