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Potential therapy of Sambiloto plant (Andrographis paniculata) using multi-compounds analysis

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Potential therapy of Sambiloto plant (*Andrographis paniculata*) using multi-compounds analysis

Terapia potencial de la planta de Sambiloto (*Andrographis paniculata*) mediante análisis de compuestos múltiples

Handayani[1a*], Wiwik Winarningsih[2a]

SUMMARY

Introduction: *Sambiloto plant (Andrographis paniculata) is often used as herbal medicine plant in Indonesia. Previous evidence indicates the use of a whole plant or single-compound approach. Analysis of multi-compounds is needed to determine the therapeutic potential for standardizing herbal medicine to provide a reliable effect.* **Methods:** *An exploratory study searching for the active content of A. paniculata was carried out in the Knapsack program. The chemical structure is analyzed computationally using Prediction of Activity Spectra for Substances (PASS) software. The analysis of the mechanism of action of drug molecules was analyzed using the Search Tool for Interacting Chemicals (STITCH) software.* **Results:** *The active content of A. paniculata is 46 types, with 5 of them having 6 effects based on chemical bonds and targeting 12 receptor proteins. Five active contents of A. paniculata include andrographidin A, caffeic acid, chlorogenic acid, wogonin 5-glucoside, and cinnamic acid. Analysis of the mechanism of action of A. paniculata based on 12 target proteins from active ingredients using a multi-compound approach shows 6 unique biological processes. Based on the chemical bonds, 5 active contents of A. paniculata have six effects, including anaphylatoxin receptor antagonist, abeta-adrenergic receptor kinase inhibitor, GABA C receptor agonist, G-protein-coupled receptor kinase inhibitor, Aryl hydrocarbon receptor agonist, and Nicotinic alpha6beta3beta4alpha5 receptor antagonist.* **Conclusion:** *There is a therapeutic potential of A. paniculata with multi-compounds analysis. A molecular docking analysis is needed to predict the affinity between the ligand (active ingredient) and the target protein.*

Keyword: *Sambiloto Plant, A. paniculata, Multi-Compounds Analysis*

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RESUMEN

Introducción: *La planta de Sambiloto (Andrographis paniculata) se utiliza a menudo como planta medicinal a base de hierbas en Indonesia. La evidencia indica el uso de la planta completa o de un solo compuesto. Se requiere de un análisis de compuestos múltiples para determinar el potencial terapéutico de estandarizar la medicina herbal para proporcionar un efecto confiable.* **Métodos:** *Se realizó un estudio exploratorio en busca del contenido activo de A. paniculata en el programa Knapsack. La estructura química se*

analiza computacionalmente utilizando el software de predicción de espectros de actividad para sustancias (PASS). El análisis del mecanismo de acción de las moléculas de fármacos se analizó mediante el software Search Tool for Interacting Chemicals (STITCH). **Resultados:** *El contenido activo de A. paniculata es de 46 tipos, de los cuales 5 tienen 6 efectos basados en enlaces químicos y se dirigen a 12 proteínas receptoras. Cinco contenidos activos de A. paniculata que incluyen andrografidina A, ácido cafeico, ácido clorogénico, wogonina 5-glucósido y ácido cinámico. El análisis del mecanismo de acción de A. paniculata basado en 12 proteínas diana de ingredientes activos utilizando un enfoque de compuestos múltiples muestra 6 procesos biológicos únicos. Según los enlaces químicos, 5 contenidos activos de A. paniculata tienen seis efectos, que incluyen un antagonista del receptor de anafilatoxina, un inhibidor del receptor quinasa betaadrenérgico, un agonista del receptor GABA-C, un inhibidor del receptor quinasa acoplado a proteína G, un agonista del receptor de hidrocarburos arilo y antagonista nicotínico del receptor alfa6-beta3-beta4-alfa5.* **Conclusión:** *Existe un potencial terapéutico de A. paniculata con el análisis de compuestos múltiples. Se necesita un análisis de acoplamiento molecular para predecir la afinidad entre el ligando (ingrediente activo) y la proteína diana.*

Palabra clave: *Planta Sambiloto, A. paniculata, Análisis de compuestos múltiples*

INTRODUCTION

Herbal medicine is used to treat tissue damage and disorders in developing countries at the molecular level including cellular signaling (1,2). Nowadays, people will return to using plant-derived compounds (3). The community generally uses herbal medicine to cure various diseases because the cost is relatively cheap and easy to reach (4). Many herbal antimicrobials have been developed to treat various diseases. Antimicrobials are mostly found in natural ingredients such as herbs and spices (5), one of them is Sambiloto (*Andrographis paniculata*) plant. This plant can be found in many places in the world, especially from India, Siam (Thailand and surrounding areas), the Malay peninsula, to the island of Java.

Sambiloto (*Andrographis paniculata*) plant is a shrub with a plant height of up to 90 cm. The leaves of the *A. paniculata* plant are used by the community to treat tuberculosis, fever, and coughs, while the stems are used to increase appetite (6).

The broad therapeutic spectrum of *A. paniculata* occurs due to the high variation in the composition of the active ingredients of this plant from various regions of the world (7). Andrographolide, neoandrographolide, deoxyandrographolide, and dehydroandrographolide were the main active ingredients of this plant based on comparisons from various regions of origin compositions differed significantly between parts of the plant (8). Several previous studies have shown that A. paniculata has anti-influenza, anti-inflammatory, antihyperglycemic, hepatoprotective, antibacterial, antiviral, antiparasitic, anticancer, immunomodulatory, and antihyperlipidemic effects, as well as cardiovascular, sexual function, and contraceptive effects (7). Safety and toxicity tests have also been carried out. Previous studies have used whole plants, and some used single-compounds. The therapeutic potential of this plant by multi-compounds analysis is still unclear and still needs further research (6,9).

Drug development can be carried out using two methods, namely drug development based on the ligand (drug molecule) characteristics and based on the structure (drug target molecule) (10). The second method can be done by single-compound or multi-compound analysis (11). Herbs can be used by consuming all the active ingredients from a part of the plant and can also be used by consuming one or several synthetic molecules inspired by the molecular composition of the herb. Determination of therapeutic potential by multi-compounds analysis is essential for herbal standardization to provide a reliable effect.

The utilization of medicinal plant databases is currently snowballing due to increasing awareness to store data related to the active ingredients of medicinal plants, one of which is Knapsack. Knapsack collects data on medicinal plant species and their metabolites and biological effects. The data that has been collected has reached 9 584 data, including 778 species data, 2 356 metabolite data, and 2 963 biological effects data (12). The chemical structure of an active ingredient in a medicinal plant can be analyzed computationally using Prediction

of Activity Spectra for Substances (PASS) software which can be accessed online (10). Analysis of the mechanism of action on drug molecules requires integrated data to achieve a complete understanding. This can be done using the Search Tool for Interacting Chemicals (STITCH), which combines various data from drug molecules, namely as many as 430 000 chemical substances (13). Receptors and their predicted effects on the active ingredients of a medicinal plant can be identified in the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) and UniProt for their function and location in cell structures to analyze their therapeutic potential (8,14). This study aims to determine the therapeutic potential of *A. paniculata* with multi-compounds analysis for herbal standardization to provide a reliable effect.

METHODS

This research is an exploratory, descriptive study with the model used in this study being *A. paniculata* regardless of the plant part. The active content data search was carried out with the keyword '*Andrographis paniculata*' in the Knapsack medicinal plant database. Each active ingredient is then identified in STITCH, including a name change according to its synonym with the corresponding name in the Knapsack. The links for each active ingredient found in STITCH are then taken to PubChem, where they are searched for the canonical SMILES code. The code is used in the PASS software to predict the biological effects. The name of the biological effect predicted by PASS is then filtered by the keyword 'receptor.' Screening is also continued until only those with a probability of activity (Pa) value of 0.7 or more remain. The receptors named in the effect names were identified in STRING and qualitatively selected for the relevant protein at each receptor. The link of each protein in STRING to UniProt was traced to determine its function and location in the cell structure. An analysis of the mechanism of action was also carried out based on the gene ontology (GO) classification shown in the pathway analysis results in STRING. Table 1 describes the distribution of variables and instruments used in this study.

RESULTS

Active Ingredients of *Andrographis paniculata*

The active content of *A. paniculata* has been identified based on the Knapsack medicinal plant database as of June 29, 2018 (Table 2). 17 of the 46 active ingredients as of that date are available for prediction with PASS. Availability refers to the availability of data in STITCH and PubChem for the SMILES canonical code.

Therapeutic Potential of *Andrographis paniculata*

The therapeutic potential of *A. paniculata* was predicted based on chemical bonding with PASS software. According to the screening criteria, there are 5 types of active ingredients with 6 types of pharmacological effects (Table 3).

Mechanism of action of *Andrographis paniculata*

The specific receptors targeted for the selected active ingredients and their functions with STRING for the human organism have been analyzed, detailed with information from UniProt (Table 4). Proteins C3AR1, C5AR1, ADRBK1, ADRBK2, GABBR1, GABBR2, GRK6, CHRNA5, CHRNA6, CHRNB3, and CHRNB4 have potential as membrane receptors that can be targets of these ingredients. AHR protein is a ligand-activated transcription factor so that it is also potential as a drug if it has a structure that can penetrate cell membranes.

The mechanism of action is a biological process based on gene ontology (GO) which involves 12 target proteins, including cell communication, signal transduction, and signalization of cell organism, particularly termination of the G-protein coupled receptor signal, complement-mediated signaling, synaptic transmission, behavioral response to nicotine, positive regulation of macrophage chemotaxis, and cell response to stimuli (Table 5).

Table 1

Division of Variables and Instruments Used

Variable	Operational Definition	Instrument	Measurement Results	Unit	Scale
Active Ingredients	Active ingredients regardless of plant parts and contained in medicinal plants that are already available in the database.	Knapsack	Name of Active Ingredients	-	Nominal
Therapeutic Potential	Potential biological effects were identified by computing chemical bond interactions based on the chemical nature of these bonds in the active ingredient represented by canonical SMILES filtered with the keyword 'receptor' and a Pa value of 0.7 or less.	PASS	Name of Effect and Active Ingredients	-	Nominal
Mechanism of Action	Classification of gene ontology for biological processes and information from UniProt on its function and location in the cell structure of proteins targeted for active ingredients (according to criteria) separately or in combination	STRING	Mechanism of Action Name and Mobile Location	-	Nominal

PASS: Prediction of Activity Spectra for Substances; STRING: Search Tool for the Retrieval of Interacting Genes/Proteins

Table 2

Active compounds of *Andrographis paniculata* based on the Knapsack Medicinal Plant Database as of June 29, 2018

No	Active Ingredients	Molecular Formula	Molecular Weight (kD)
1	Caffeic acid	C9H8O4	180.04225874
2	Cinnamic acid	C9H8O2	148.0524295
3	3-O-Caffeoylquinic acid	C16H18O9	354.09508217
4	14-Acetylandrographolide	C22H32O6	392.21988875
5	Andrograpanin	C20H30O3	318.21949482
6	Neoandrographolide	C26H40O8	480.27231825
7	14-Deoxy-11-oxoandrographolide	C20H28O5	348.193674
8	Andrographic acid	C20H28O6	364.18858863
9	Bisandrographolide B	C40H56O8	664.39751876
10	12S-Hydroxyandrographolide	C20H32O6	368.21988875
11	Andrographolide	C20H30O5	350.20932407
12	Andrographiside	C26H40O10	512.2621475
13	14-Deoxyandrographolide	C20H30O4	334.21440945
14	Wogonin 5-glucoside	C22H22O10	446.12129692
15	Ferulic acid	C10H10O4	194.05790881
16	Andrographidin A	C23H26O10	462.15259705
17	Dihydroskullcap flavone I	C17H16O6	316.09468824
18	7-O-Methylwogonin	C17H14O5	298.08412356
19	Isoandrographolide	C20H30O5	350.20932407
20	Apigenin 7,4'-dimethyl ether	C17H14O5	298.08412356
21	(-)-beta-Sitosterol	C29H50O	414.38616622
22	5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone	C19H18O8	374.10016755
23	5-Hydroxy-7,8-dimethoxyflavone 5- glucoside	C23H24O10	460.13694699
24	5-Hydroxy-7,8,2'-trimethoxyflavone 5-glucoside	C24H26O11	490.14751167
25	5,2',3'-Trihydroxy-7,8-dimethoxyflavone 3'-glucoside	C23H24O12	492.12677623
26	5-Hydroxy-7,8,2',3'-tetramethoxyflavone 5-glucoside	C25H28O12	520.15807636
27	5,4'-Dihidroxy-7,8,2',3'-tetramethoxy flavone 5-glucoside	C25H28O13	536.15299098
28	5-Hydroxy-3,7,8,2'-tetramethoxyflavone	C19H18O7	358.10525293
29	5-Hydroxy-7,8-dimethoxyflavanone	C17H16O5	300.09977362
30	Paniculide A	C15H20O4	264.13615913
31	Paniculide B	C15H20O5	280.13107375
32	Paniculide C	C15H18O5	278.11542369
33	5-Hydroxy-7,2',6'-trimethoxyflavone	C18H16O6	328.09468824
34	Skullcapflavone 1,2'-O-beta-D-glucopyranoside	C23H24O11	476.13186161
35	Ninandrographolide	C26H40O9	496.26723288
36	14-Deoxy-11,14-didehydroandrographolide	C20H28O4	332.19875938
37	14-Acetyl-3,19-isopropylideneandrographolide	C25H36O6	432.25118888
38	5,7,2',3'-Tetramethoxyflavanone	C19H20O6	344.12598837
39	12R,13R-Hydroxyandrographolide	C20H32O6	368.21988875
40	12S,13S-Hydroxyandrographolide	C20H32O6	368.21988875
41	7R-Hydroxy-14-deoxyandrographolide	C20H30O5	350.20932407
42	7S-Hydroxy-14-deoxyandrographolide	C20H30O5	350.20932407
43	14-Deoxy-17-hydroxyandrographolide	C20H32O5	352.22497413
44	3-O-beta-D-Glucopyranosylandrographolide	C26H40O10	512.2621475
45	Andropanolide	C20H30O5	350.20932407
46	Bisandrographolide C	C40H56O8	664.39751876

Table 3

Therapeutic potential of *Andrographis paniculata* based on Chemical Bonding with PASS Software According to Screening Criteria*

No.	Effects	Active Ingredients	Pa Value**
1	Anaphylatoxin receptor antagonist	Andrographidin A	0.906
2	Beta-adrenergic receptor kinase inhibitor	Caffeic acid	0.789
3	Beta-adrenergic receptor kinase inhibitor	Chlorogenic acid	0.716
4	GABA C receptor agonist	Caffeic acid	0.744
5	G-protein-coupled receptor kinase inhibitor	Caffeic acid	0.789
6	G-protein-coupled receptor kinase inhibitor	Chlorogenic acid	0.716
7	Anaphylatoxin receptor antagonist	Wogonin 5-glucoside	0.944
8	Aryl hydrocarbon receptor agonist	Wogonin 5-glucoside	0.769
9	Beta-adrenergic receptor kinase inhibitor	Cinnamic acid	0.826
10	GABA C receptor agonist	Cinnamic acid	0.8
11	G-protein-coupled receptor kinase inhibitor	Cinnamic acid	0.826
12	Nicotinic alpha6beta3beta4alpha5 receptor antagonist	Cinnamic acid	0.759

PASS: Prediction of Activity Spectra for Subtances;
* = available on STITCH, contains the text 'receptor', and Pa value >0.7
** = probability of activity

Table 4

Mechanism of action of A. paniculata based on data available on STRING as of 29 June 2018 along with subcellular functions and locations for analysis of potential as membrane receptors based on UniProt

No.	Effects	Protein (gene/short name)	Subcellular Location
1	Anaphylatoxin receptor antagonist	Complement component 3a receptor 1 (C3AR1)	Cell membrane
2	Anaphylatoxin receptor antagonist	Complement component 5a receptor 1 (C5AR1)	Cell membrane
3	Aryl hydrocarbon receptor agonist	Aryl hydrocarbon receptor (AHR)	Cytoplasm
4	Beta-adrenergic receptor kinase inhibitor	Adrenergic, beta, receptor kinase 1 (ADRBK1)	Beta-adrenergic receptor kinase inhibitor
5	Beta-adrenergic receptor kinase inhibitor	Adrenergic, beta, receptor kinase 2 (ADRBK2)	Cell membrane
6	GABA C receptor agonist	Gamma-aminobutyric acid (GABA) B receptor, 1 (GABBR1)	Postsynaptic cell membrane; secreted
7	GABA C receptor agonist	Gamma-aminobutyric acid (GABA) B receptor, 2 (GABBR2)	Postsynaptic cell membrane
8	G-protein- coupled receptor kinase inhibitor	G protein-coupled receptor kinase 6 (GRK6)	Cell membrane
9	Nicotinic alpha6beta3beta4 alpha5 receptor antagonist	Cholinergic receptor, nicotinic, alpha 6 (neuronal) (CHRNA6)	Postsynaptic cell membrane
10	Nicotinic alpha6beta3beta4 alpha5 receptor antagonist	Cholinergic receptor, nicotinic, beta 3 (neuronal) (CHRNB3)	Postsynaptic cell membrane
11	Nicotinic alpha6beta3beta4 alpha5 receptor antagonist	Cholinergic receptor, nicotinic, beta 4 (neuronal) (CHRNB4)	Postsynaptic cell membrane
12	Nicotinic alpha6beta3beta4 alpha5 receptor antagonist	Cholinergic receptor, nicotinic, alpha 5 (neuronal) (CHRNA5)	Postsynaptic cell membrane

STRING: Search Tool for the Retrieval of Interacting Genes/Proteins

Table 5

Mechanism o action of *Andrographis paniculata* based on pathway analysis of 12 target proteins with STRING as of 29 June 2018 in the form of biological processes according to gene ontology (GO) classification

No.	Pathway ID	Pathway Description	Count in Gene Set	False Discovery Rate
1	GO:0007154	Cell communication	11	0.00197
2	GO:0007165	Signal transduction	11	0.00197
3	GO:0044700	Single organism signaling	11	0.00197
4	GO:0038032	Termination of G-prot. coupled receptor signaling pathway	3	0.00384
5	GO:0002430	Complement receptor mediated signaling pathway	2	0.00621
6	GO:0007268	Synaptic transmission	5	0.0114
7	GO:0002430	Complement receptor mediated signaling pathway	2	0.00621
8	GO:0007268	Synaptic transmission	5	0.0114
9	GO:0035095	Behavioral response to nicotine	2	0.0114
10	GO:0010759	Positive regulation of macrophage chemotaxis	2	0.0142

STRING: Search Tool for the Retrieval of Interacting Genes/Proteins

The result of the false discovery rate was <0.05. It can be concluded that the results of this study were valid/significant.

DISCUSSION

A. paniculata is one of the most popular and important medicinal plants in East and Southeast Asia. This plant is widely mentioned in various Indian, Chinese, Malay, Unani, and Japanese medical systems. Various studies have shown the effects of *A. paniculata* content as anti-cancer, anti-inflammatory, anti-diabetic, anti-hypertensive, anti-toxin, cholestatic, hepatoprotective, anti-thrombotic, anti-retroviral, anti-microbial, anti-pyretic, anti-malarial, antioxidant, immunomodulatory, and cardioprotective effects. The main active principle contributing to the biological activity is diterpene lactones, but flavonoid derivatives, xanthones, and caffeic acid also contribute to the anti-oxidative, anti-proliferative, anti-atherosclerosis, and anti-malarial effects (15,16). Another study also supports the results of this study which states that *A. paniculata* extract has antimalarial activity both in vitro and in vivo (16).

Based on the results of our analysis, the active ingredients of *A. paniculata* are 46 types, 5 of which are andrographidin A, caffeic acid, chlorogenic acid, wogonin 5-glucoside, and cinnamic acid. These five active ingredients based on their chemical bonds have six effects, namely: anaphylatoxin receptor antagonist, a beta-adrenergic receptor kinase inhibitor, GABA C receptor agonist, G-protein-coupled receptor kinase inhibitor, Aryl hydrocarbon receptor agonist, and Nicotinic alpha6beta3beta4alpha5 receptor antagonist. These five active ingredients target 12 receptor proteins with potential therapeutic potential: C3AR1, C5AR1, AHR, ADRBK1, ADRBK2, GABBR1, GABBR2 GRK6, CHRNA5, CHRNA6, CHRNB3, and CHRNB4.

Anaphylatoxins are protein fragments that are formed when the complement system is activated.

Anaphylatoxins can trigger the degranulation of endothelial cells, mastocytes, and phagocytes, which further trigger an inflammatory response. Therefore, the effect of the anaphylatoxin receptor antagonist on this bitter plant is predicted to have the ability as an anti-inflammatory therapeutic agent (17). The Pa values of 0.906 for the active ingredient andrographidin A and 0.944 for wogonin 5-glucoside indicated that the bitter plant has a strong effect as an anaphylatoxin receptor antagonist.

Cinnamic acid is one of the active ingredients of the bitter plant (*A. paniculata*), which has a strong effect as a beta-adrenergic receptor kinase inhibitor (Pa = 0.826), GABA C receptor agonist (Pa = 0.8), and G-protein-coupled receptor kinase inhibitors (Pa = 0.826). Beta-adrenergic receptor kinase inhibitors and G-protein-coupled receptor kinase inhibitors have therapeutic effects related to cardiovascular function (heart failure, hypertension, cardiac hypertrophy) and metabolic homeostasis (obesity, type-2 diabetes, NAFLD) (18). Meanwhile, the GABA C receptor agonist has sedative, hypnotic effects and anti-convulsion (anti-seizure) properties (19).

The mechanism of action in the form of biological processes according to GO classification that can be played with the 12 target proteins is explicitly the termination of the G-protein coupled receptor signal, complement-mediated signaling, synaptic transmission, behavioral response to nicotine, positive regulation of macrophage chemotaxis, and cell response to stimuli. Based on the results of the analysis of the mechanism of action of the 12 target proteins, the false discovery rate value was <0.05. This indicates that the results of the analysis were valid/significant.

CONCLUSION

Forty-six active compounds of *A. paniculata* have been identified based on the Knapsack medicinal plant database as of June 29, 2018. There are five types of active compounds with six types of therapeutic potential of *A. paniculata* predicted based on chemical bonds with PASS software. According to GO classification, analysis of the mechanism of action of *A. paniculata* based on 12 target proteins of the active ingredient using a multi-compound approach showed six specific biological processes. Molecular docking analysis needs to be done to predict the affinity between the ligand (active content) and the target protein.

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