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Computational Study of Bioactive Components of Sweet Basil (*Ocimum basilicum Linn.*), Luyang dilaw (*Curcuma longa Linn.*) and Lagundi (*Vitex negundo*) as Inhibitor against Human Immunodeficiency Virus (Hiv-1)

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ABSTRACT

Human Immunodeficiency Virus (HIV-1) has glycoproteins gp41 and gp120 use to attached to the host cell. Development of antiviral drug use in silico drug design to select potent lead molecule from medicinal plants. Bioactive components of Sweet basil (*Ocimum basilicum Linn.*), Luyang dilaw (*Curcuma longa Linn.*), Lagundi (*Vitex negundo*) were used as ligands to inhibit HIV-1 gp120 and gp41 using ArgusLab Software. Inhibition of gp120, results showed that the α-Guaiene from Sweet basil has the lowest binding affinity and energy fitness which, are-9.6kcal/mol and -8.6kcal/mol, respectively. Sitosterol from Sweet basil has the lowest binding affinity and energy fitness of -10.9kcal/mol and -10.58kcal/mol for the inhibition of gp41. Statistical analysis shows that these bioactive components are comparable with that of the active component of commercially available drugs in inhibiting gp120 and gp41 based on these parameters. Thus, these bioactive compounds may be developed further as drugs in inhibiting HIV-1.

Keywords: In silico, HIV-1 glycoproteins, Arguslab, Sweet basil (*Ocimum basilicum Linn.*), Luyang dilaw (*Curcuma longa Linn.*), Lagundi (*Vitex negundo*).

INTRODUCTION

Human immunodeficiency virus (HIV) infects cells of the immune system, which results in progressive deterioration of the immune system. Infection of this virus leads to "immune deficiency" wherein the immune system can no longer fulfill its role of fighting infection and disease[1]. Department of Health of the Philippines records a total of 6,552 people who were diagnosed with HIV in 2015. The figure was 37 percent higher than the total number of HIV incidence for the entire 2001. There are now a total of 29,079 HIV/AIDS cases in the country since the first case diagnosed in 1984. Most of the cases with a total of 24,655 were recorded in the last five years. This continuous increase in HIV/AIDS cases lead to its inclusion in the list of priority diseases worldwide[2].

Human immunodeficiency virus primarily targets immune cells. The virus attached to the host cell through glycoprotein gp120 after which, transmembrane glycoprotein gp41 mediates membrane fusion to complete the entry of the virus to the host cell[3]. The importance of these glycoprotein receptors to viral infection made them targets of researches in developing drugs for the disease.

Increasing costs of drug developments have been a growing concern in discovering new drugs. Thus, there is a need for the use of alternative tools in determining the efficacy and safety of drugs at minimum time and lower cost. One of which is the use of In silico drug design or computer-aided drug design (CADD). It plays a significant role in all stages of drug development from the preclinical discovery stage to late-stage clinical development. It aids in the selection of potent lead molecule and prevention of late-stage clinical failures[4]. Arguslab is a licensed freeware that offers a graphical user interface with ease of use in molecular docking[5]. The docking efficiency of this program was validated and found to be useful for virtual screening[6]. It was used in screening drugs against several priority diseases like malaria[7], influenza virus[9,10], cancer[11,12], dengue[13], and against herpesvirus[14].

Natural products and their derivatives have been recognized as a source of therapeutic agents. Bioactive components of plants have no side effects than synthetic drugs because they accumulate within living cells[15]. Thus, plant-based medicines are considered to be safer, non-toxic, and less harmful than synthetic drugs.

Several traditionally used natural products were determined to contain anti-HIV bioactive components. Lagundi, one of the approved herbal medicine of DOH, contains Betulinic acid, ursolic acid, and β-sitosterol, possess antifeedant, antibacterial, anti-cancer, anti-HIV, and angiogenic properties[16]. Curcumin as a modest inhibitor of HIV-1 (IC_{50} = 100 mM) and HIV-2 (IC_{50} = 250 mM) proteases[17]. The anti-HIV-1 activity of pure compounds isolated from aerial part extracts of *Ocimum basilicum* was also found. The Antiviral activity of 500 µg/ml eugenol and eugenol epoxide isolated from this plant inhibit viral replication greater than 90%[18].

In support of the advancement in greener chemistry in minimizing the amount of chemical used in researches to promote healthier people and environment, in silico screening of bioactive components of Sweet basil, Luyang dilaw, and Lagundi for potential inhibitors of important glycoproteins of HIV-1 was done.

MATERIALS AND METHODS

Crystal structures of HIV-1 gp120 and gp41 were retrieved from Protein Data Bank with PDB ID: 1G9M and 1AIK (https://www.rcsb.org/). The structures of gp120 and gp41 were obtained in X-ray crystals and refined at the resolutions of 2.5Å and 2.0 Å, respectively[19,20]. The active site is determined for HIV-1 gp120 with the following amino acids Gly 473, Trp 427 Val 430, Asn 377, Ser 375, Asp368 and for gp41 are Leu 565, Leu 566, Leu 576, Thr 569, Val 570, Trp 571, Gly 572, Ile 573, Lys 574, Gln 577[21,20]. Molecular structures of 29 bioactive components found in Sweet basil (*Ocimum basilicum Linn.*)[22], Luyang dilaw (*Curcuma longa Linn.*)[23], Lagundi (*Vitex negundo*)[24] were used in this study and structures of commercially available drug which is Fostemsavir against gp 120[25] and Enfuvirtide against gp41[26] were obtained from www.chemspider.com. The structures of bioactive components for each plant and control are in MOL file format and then transferred to ArgusLab[27] software (http://www.arguslab.com/) to optimize the geometry of the structures.

The active site-directed docking was performed in ArgusLab software using a Lamarckian Genetic Algorithm with a binding site bounding box size of 16.665x12.03x20.373 angstrom and a grid resolution of 0.4 angstroms. The binding energies and search algorithms of energy fitness for the best pose were obtained in kcal/mol. The bounded amino acid residue was determined to identify to which amino acid in the active site does the bioactive components attached.

A total of three docking calculation trials were conducted. The data for binding affinity and energy fitness were exploited in Excel software to analyze using a t-test with a P-value under 0.05 was considered as the significance level.

RESULTS AND DISCUSSION

Twenty-nine bioactive components of each plant were bonded to the active site of HIV-1 gp120 and gp41. The results of the binding affinity of bioactive components of Sweet basil (*Ocimum basilicum Linn.*), Luyang dilaw (*Curcuma longa Linn.*) and Lagundi (*Vitex negundo*) to the active site of HIV-1 gp120 and gp41 was shown at in Table 1. The binding affinity is the sum of the final intermolecular energy and the torsion-free energy. The negative value of binding affinity depicts that the reaction between the bioactive component bonded to the active site occurs spontaneously due to this change in total intermolecular and torsional energies. Thus, a high negative value of binding affinity corresponds to better bonding of bioactive components with the glycoproteins; better inhibition of the virus. The binding affinity of the best inhibitor bonded in gp120 are -9.62 kcal/mol α-guaiene from Sweet Basil, -8.72kcal/mol Sabinene from Luyang Dilaw and -6.39kcal/mol 1,8-Cineole from Lagundi. The binding affinity of the best inhibitor against gp41 is -10.99kcal/mol Sitosterol from Sweet basil, -9.57kcal/mol Bisabolene from Luyang Dilaw, and -10.11kcal/mol Betulinic Acid from Lagundi. These values were statistically determined to have no significant difference with that of the positive control.

Table 1: Binding Affinity of Bioactive components of Sweet basil (*Ocimum basilicum Linn.*) Luyang dilaw (*Curcuma longa*) and Lagundi (*Vitex negundo*) to gp120 and gp41. The value with ▶ is the lowest binding affinity among the bioactive components present in each plant

Sweet basil (*Ocimum basilicum Linn.*)	Binding Affinity (kcal/mol) against		Luyang dilaw (*Curcuma longa*)	Binding Affinity (kcal/mol) against		Lagundi (*Vitex negundo*)	Binding Affinity (kcal/mol) against	
	gp120	gp41		gp120	gp41		gp120	gp41
Apigenin	-4.08	-7.05	a-thujene	-7.84	-8.02	1,8-cineole	▶-6.39	-7.01
Bornyl acetate	-2.69	-7.56	a-pinene	-6.85	-7.86	Agnuside	20.6	-7.29
Cadinene	-7.93	-8.62	borneol	-6.13	-7.92	Betulinic Acid	166.4	▶-10.11
Campesterol	149.4	-9.05	limonene	-8.49	-9.08	Caryophyllene epoxide	3.69	-9.30
Camphene	-7.22	-7.31	2-carene	-7.33	-7.54	Casticin	11.2	-6.68
Carvacnol	-5.93	-7.21	4-terpineol	-4.93	-7.47	Chrysosplenol D	10.12	-6.18
Circimaritin	-1.3	-7.00	a-phellandrene	-6.02	-8.61	Coniferyl aldehyde	-5.03	-6.40
Cirsilineol	19.72	-6.69	a-terpinene	-7.43	-8.65	Corymbosin	11.47	-6.47
Cubenol	-0.25	-8.14	atlantone	-7.01	-9.02	Germacrene D	0.54	-9.17
Eucalyptol	-3.77	-6.67	Bisabolene	-8.5	▶-9.57	oleanolic acid acid	159.3	-9.35
Eugenol	-4.78	-6.69	bisdesmethoxycurcumin	0.47	-8.89	Isofraxidin	-3.3	-6.10
Germacrene D	4.29	-9.19	b-ocimene	-7.73	-8.44	Isoorientin	14.78	-6.69
Isothylmusin	11.39	-6.42	cineol	-2.61	-7.31	Isorhamnetin	11.89	-6.80
Linalool	-5.57	-7.43	citral	-4.7	-7.71	Kaempherol	22.88	-6.75
Luteolin	-1.81	-6.52	curcumin II	129.3	-8.78	Linalool	-3.82	-8.11
Methyl eugenol	-3.99	-7.38	Curcumin III	25.84	-8.78	Luteolin	-3.07	-6.68
Orientin	46.76	-6.35	cyclocurcumin	14.58	-7.88	Negundin B	10.08	-8.23
Sitosterol	362.7	▶-10.99	desmethoxycurcumin	38.07	-7.88	Negundoain A	61.04	-8.18
Stigmasterol	345.4	-9.60	dihydrocurcumin	15.36	-7.79	Negundoside	37.78	-6.94
Tau-cadinol	-3.71	-8.78	iso-artemisia ketone	-6.77	-7.98	Negunferol	2.89	-7.40
Ursolic acid	146.6	-10.34	myrcene	-6.7	-9.19	Pinoresinol	23.8	-7.13
α-bergamotene	1.95	-8.80	neral	-6.77	-8.00	Quercetin	10.29	-5.44
α-bisabolol	-5.82	-8.28	Sabinene	▶-8.72	-8.33	Secoisolariciresinol diglycoside	821.1	-5.24
α-copaene	3.75	-8.35	sesquiphellandrene	-3.28	-8.63	Sesamin	27.03	-6.82
α-guaiene	▶-9.62	-8.96	sesquiterpenes	0.1	-7.70	Vitedoin B	69.29	-7.49
α-gurjunene	2.71	-8.32	terpineol	-2.11	-7.39	Vitexdoin D	24.51	-7.28
α-pinene	-3.19	-7.51	thymol	-7.37	-7.49	Vitrofolal E	44.28	-7.95
β-elemene	-2.5	-8.22	tumeron	-7.38	-8.66	▶-guaiene	-0.53	-8.59
β-farnesene	0.44	-9.13	zingiberene	-4.37	-8.20	▶-pinene	4.03	-7.53

Positive control for the inhibition of gp120: Fostemsavir32.40686 kcal/mol

Positive control for the inhibition of gp120: Enfuvirtide-1.196527667 kcal/mol

Table 2: Energy Fitness of Bioactive components of Sweet basil (*Ocimum basilicum Linn.*) Luyang dilaw (*Curcuma longa*) and Lagundi (*Vitex negundo*) to gp120 and gp41. The value with ▶ is the lowest binding affinity among the bioactive components present in each plant

Sweet basil (*Ocimum basilicum Linn.*)	Energy Fitness (kcal/mol) against		Luyang dilaw (*Curcuma longa*)	Energy Fitness (kcal/mol) against		Lagundi (*Vitex negundo*)	Energy Fitness (kcal/mol) against	
	gp120	gp41		gp120	gp41		gp120	gp41
Apigenin	-5.95	-6.66	a-thujene	-8.18	-8.55	1,8-cineole	-5.11	-7.85
Bornyl acetate	-4.64	-7.49	a-pinene	-5.04	-7.94	Agnuside	7.47	-6.66
Cadinene	-6.51	-9.31	borneol	-4.95	-7.94	Betulinic Acid	157.67	▶-10.35
Campesterol	64.75	-9.71	limonene	-7.79	-9.22	Caryophyllene epoxide	7.66	-9.36
Camphene	-5.38	-7.43	2-carene	-7.43	-8.92	Casticin	1.64	-6.76
Carvacnol	-7.91	-7.21	4-terpineol	-4.66	-7.75	Chrysosplenol D	21.27	-6.36
Circimaritin	-2.12	-6.89	a-phellandrene	-7.20	-9.18	Coniferyly aldehyde	-4.59	-6.47
Cirsilineol	7.31	-6.39	a-terpinene	-6.22	-8.12	Corymbosin	13.81	-6.15
Cubenol	5.63	-8.19	atlantone	-7.44	-9.54	Germacrene D	-1.35	-9.05
Eucalyptol	-1.97	-7.12	Bisabolene	-7.98	-9.61	oleanolic acid acid	231.63	-9.73
Eugenol	-4.77	-7.37	bisdesmethoxycurcumin	-4.49	-9.59	Isofraxidin	-5.46	-6.20
Germacrene D	0.97	-8.60	b-ocimene	▶-8.18	-8.25	Isoorientin	30.25	-6.72
Isothylmusin	33.17	-5.75	cineol	-3.52	-6.75	Isorhamnetin	5.98	-7.10
Linalool	-4.48	-6.83	citral	-7.01	-7.82	Kaempherol	9.80	-6.77
Luteolin	-4.49	-6.52	curcumin II	29.75	-8.66	Linalool	▶-6.14	-7.74
Methyl eugenol	-4.56	-7.40	Curcumin III	18.83	-8.25	Luteolin	-2.66	-7.07
Orientin	25.89	-5.21	cyclocurcumin	19.80	-7.58	Negundin B	7.20	-7.81
Sitosterol	110.29	▶-10.58	desmethoxycurcumin	-3.67	-8.41	Negundoain A	73.02	-8.00
Stigmasterol	205.14	-10.15	dihydrocurcumin	11.22	-8.37	Negundoside	55.18	-7.02
Tau-cadinol	-4.47	-8.20	iso-artemisia ketone	-5.82	-8.26	Negunferol	13.41	-6.91
Ursolic acid	120.49	-9.17	myrcene	-7.91	-8.34	Pinoresinol	10.99	-6.67
α-bergamotene	5.28	-8.48	neral	-7.01	-7.15	Quercetin	4.58	-6.31
α-bisabolol	-7.30	-8.56	Sabinene	-6.62	-7.90	Secoisolariciresinol diglycoside	460.44	-6.68
α-copaene	0.57	-8.74	Sesquiphellandrene	-3.57	▶-10.12	Sesamin	16.79	-7.30
α-guaiene	▶-8.64	-8.19	sesquiterpenes	7.55	-8.84	Vitedoin B	166.93	-7.56
α-gurjunene	6.78	-8.39	terpineol	-1.50	-7.60	Vitexdoin D	26.05	-7.34
α-pinene	-5.27	-7.87	thymol	-7.80	-7.83	Vitrofolal E	21.69	-7.48
β-elemene	7.14	-8.84	tumeron	-7.29	-8.09	▶-guaiene	-2.67	-8.65
β-farnesene	-1.79	-8.70	zingiberene	-5.49	-8.09	▶-pinene	12.18	-7.59

Positive control for the inhibition of gp120: Fostemsavir96.67143333 kcal/mol

Positive control for the inhibition of gp120: Enfuvirtide56.42116667 kcal/mol

Energy Fitness is the final intermolecular energy and the final energy of the bioactive components after it is bounded to the amino acid residues of the active site. The lower the energy fitness of the bioactive components bonded to gp120 and gp41 means, the more stable it is after the reaction. Table 2 shows the energy fitness of bioactive components of sweet basil (*Ocimum basilicum Linn.*) Luyang dilaw (*Curcuma longa*) and Lagundi (*Vitex negundo*) bonded to gp120 and gp41. The lowest energy fitness among the bioactive components in each of the three plants bonded to gp120 is -8.64 kcal/mol α-Guaiene from Sweet Basil, -8.18 kcal/mol B-Ocimene from Luyang Dilaw and -6.14 kcal/mol Linalool from lagundi. The results of the energy fitness of the bioactive component bonded to gp41 are -10.58 kcal/mol Sitosterol from Sweet Basil, -10.11 kcal/mol Sesquiphellandrene from Luyang Dilaw and -10.35 kcal/mol Betulinic acid from Lagundi. These values were statistically determined to be comparable with that of the positive control.

Determining the amino acid residues of the active site where the inhibitors attached can help in the development of an antiviral drug. It provides data on how to modify the structure of the inhibitor for enhancing its bonding with the glycoproteins. The amino acid residues of the active site of HIV-1 gp120 and gp41 bounded to the bioactive components

determined based on binding affinity and energy fitness. The bioactive compounds form a bridging bond in the backbone carbonyls of Gly 473 and Trp 427, which corresponds to successful docking and inhibition of gp120[20,28]. Most of the bioactive components bounded to Ile 573, Leu 576, Leu 566, Lys 574, and Thr 569 amino acid residues of the active site of HIV-1 gp4.

CONCLUSION

The bioactive components of Sweet basil (*Ocimum basilicum Linn*.), Luyang dilaw (*Curcuma longa Linn*.) and Lagundi (*Vitex negundo*) were bonded to the active site of HIV-1 gp120 and gp41 to inhibit the attachment of the virus to the host. Among the 29 bioactive components on each of the three plants, α-guaiene from Sweet basil (*Ocimum basilicum Linn*.), Sabinene, and b-Ocimene from Luyang dilaw (*Curcuma longa Linn*.) and 1,8-cineol and Linalool from Lagundi (*Vitex negundo*) were determined to be the best inhibitor candidates against gp120. For the inhibition of gp41, the following found to be the best inhibitor candidates among the bioactive components, Sitosterol from Sweet basil (*Ocimum basilicum Linn*.), Bisabolene and Sesquiphellandrene Luyang dilaw (*Curcuma longa Linn*.) and Betulinic acid from Lagundi (*Vitex negundo*). Determined best inhibitors are bounded to the Gly 473 and Trp 427 for the inhibition of gp120 and bounded to Ile 573, Leu 576, Leu 566, Lys 574 and, Thr 569 to inhibit gp41.

Based on these parameters, the best inhibitor candidates were determined to be statistically comparable with the active component of the commercially available drugs against HIV. Thus, these bioactive components can be further isolated from the medicinal plants and modified for drug development.

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Conflict of Interest

The authors declare that there is no conflict of interest in this work with regards to publication.

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