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Article

Molecular docking of Vitamin D3 Receptor (VDR) with potential herbal substance as ligand to prevent excessive hair loss in menopausal women

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Abstract : Hair loss is commonly found in menopausal women. Hair loss is one of the consequences of hormonal dynamics when a woman stops having menstrual cycle, which affect calcium and vitamin D level in the body. Although it is clear enough that hormonal adjustment is required, older people and another sociodemographic factor prefer herbal-based therapeutic rather than synthetic-based due to tradition and positive experience factors. This study is an in-silico study which aims to point out the possible ligand candidates that can work as Vitamin D Receptor (VDR) agonists. We perform molecular docking using Autodock version 4.2 with the criteria of Lamarckian GA. VDR (PDB ID: 1TXI) was docked with ten compounds and one native ligand, then analyzed using Autodock 4.2. Dolichosterone, Gartanin, and (-)-Matairesinol, Luteolin, 5-HETE, Sinapyl glucoside, and geraniol, in order shows smallest to bigger binding energy when simulated in the software (-9.72, -7.70, -7.20, -6.88, -5.76, -5.71 kcal/mol). Thus, we found that these compounds are potential to become VDR agonist. Further research is still required to determine each compound drug potential and maximize therapeutic concentration for medicinal purposes.

Keywords: Vitamin D receptor, docking, herbal, hair loss, menopause.

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1. Introduction

Hair loss is one of the usual findings when women grow older. Ranging from 20-60%, women before reaching the age of 60 years suffer from this hair loss.[1] In addition to hair loss, eyebrow loss is also a problem in women older than 60 years.[2] Hair loss in menopausal women mainly caused by lower sex hormone level in blood, such as estrogen and testosterone. Other factors associated with is scalp sebum level, thyroid-stimulating hormone, hemoglobin, genetic factors, and stress level.[3] Hair loss caused a significant impact on the patient's quality of life, so prevention and treatment are needed.[4]

Vitamin D Receptor (VDR) is a receptor protein located in the cell nucleus. VDR itself is distributed in all body cells, mainly concentrated in the digestive tract and kidneys. When activated by Vitamin D3, VDR acts as a significant regulator of calcium homeostasis, bone mineralization, and proliferation and modulation of the immune system. In addition, VDR also controls the expression of various genes related to the transport, bioactivation, and detoxification of endogenous compounds and xenobiotics, including drugs. The physiological agonist of VDR is the active form of vitamin D, also known as calcitriol or 1α,25-dihydroxyvitamin D3.[5]

Physiologically, during the pre-menopausal period in women, blood levels of estrogen decrease accompanied by a natural increase in androgen concentrations, leading to androgenic hair loss.1 These changes also lead to decreased vitamin D levels, which plays a role in maintaining the cycle of hair follicle differentiation. A study in Japan showed that

the administration of 200,000 IU of vitamin D3 resulted in significant improvement in hair loss ($p < 0.0003$; $r = 0.457$) in adult women with vitamin D levels below the average threshold.4 These findings further strengthen the Calcitriol-VDR complex level essential in preventing hair loss.[1,2,6]

Indonesia is home to 25% of flora species from all over the world. This biodiversity prospecting high potential for the manufacture of novel herbal medicines.[7] Herbal products themselves are also more accepted in treating mild to moderate diseases than synthetic drugs with the reason of disappointment of usual treatment, past positive experiences, and traditional aspect.[8] Factors associated with high preferences towards herbal medicine especially in developed countries including health status, high plant medicinal knowledge, and religional view on herbal medicine.[9] Meanwhile, Molecular docking simulations were countlessly conducted as the preliminary experiment to determine possibility of a compound to molecularly interacted to each other. Therefore, our study aims to conduct molecular docking experiments on VDR with the HerbalDb database to determine the potential of herbal compounds that can act as agonists for VDR.

2. Results and Discussion

From pharmacophore modeling, the Vitamin D receptor (PDB ID: 1TXI) has one native ligand, Inecalcitol (PDB ID: TX5). The pharmacophore binding site has also been identified, i.e., ARG274, SER237, HIS305, HIS397, ALA231, LEU227, VAL418, LEU414, VAL234, VAL300, LEU313, LEU309, MET272, LEU230, ILE268, LEU233, TRP286, ILE271, SER278, and TYR143. Figure 3a and 3b shows the pharmacophore interaction between the native ligand and Dolichosterone as one of the possible VDR ligand with lowest binding energy. The current possible ligand candidates chosen were analyzed with Lipinski's Rule of Five properties. The compound sorted according to their binding energy, from smallest to biggest. From the simulations, dolichosterone shows the lowest binding energy from the list of possible ligands of vitamin D receptor with no Violation of Lipinski's rule. From the possible ligands retrieved, Glucobrassicin is the only compound that have violation on Lipinski's role in hydrogen bond donor aspect. Gartanin, (-)-Matairesinol, Luteolin, 5-HETE, 9-ribosyl-cis-zeatin, Sinapyl glucoside, 9-ribosyl-trans-zeatin, and Geraniol, sequentially shows possibilty of becoming vitamin D receptor from the aspect of binding energy and no violation of Lipinski's rule shown in Table 1.

Table 1. Lipinski's Rule of Five Properties of Vitamin D Receptor Potential Agonists

No	Compound	Binding Energy (kcal/mol)	Lipinski's Rule of Five Parameter				
			Molecular Weight (<500 Da)	LogP (<5)	H-bond donor (<5)	H-Bond acceptor (<10)	Violation
1	Native ligand	-13.02	402.6	4.60	3	3	0
2	Dolichosterone	-9.72	462.66	3.69	4	5	0
3	Gartanin	-7.70	396.43	4.31	4	6	0
4	(-)-Matairesinol	-7.20	358.39	2.75	2	6	0
5	Luteolin	-6.88	286.24	1.73	4	6	0
6	Glucobrassicin	-5.76	448.47	-0.45	6	10	1
7	5-HETE	-5.71	320.47	4.74	2	3	0
8	9-ribosyl-cis-zeatin	-5.61	351.36	-0.73	5	8	0
9	Sinapyl glucoside	-5.60	370.35	-0.34	4	9	0
10	9-ribosyl-trans-zeatin	-5.43	351.36	-0.73	5	8	0
11	Geraniol	-4.96	154.25	1.73	1	1	0

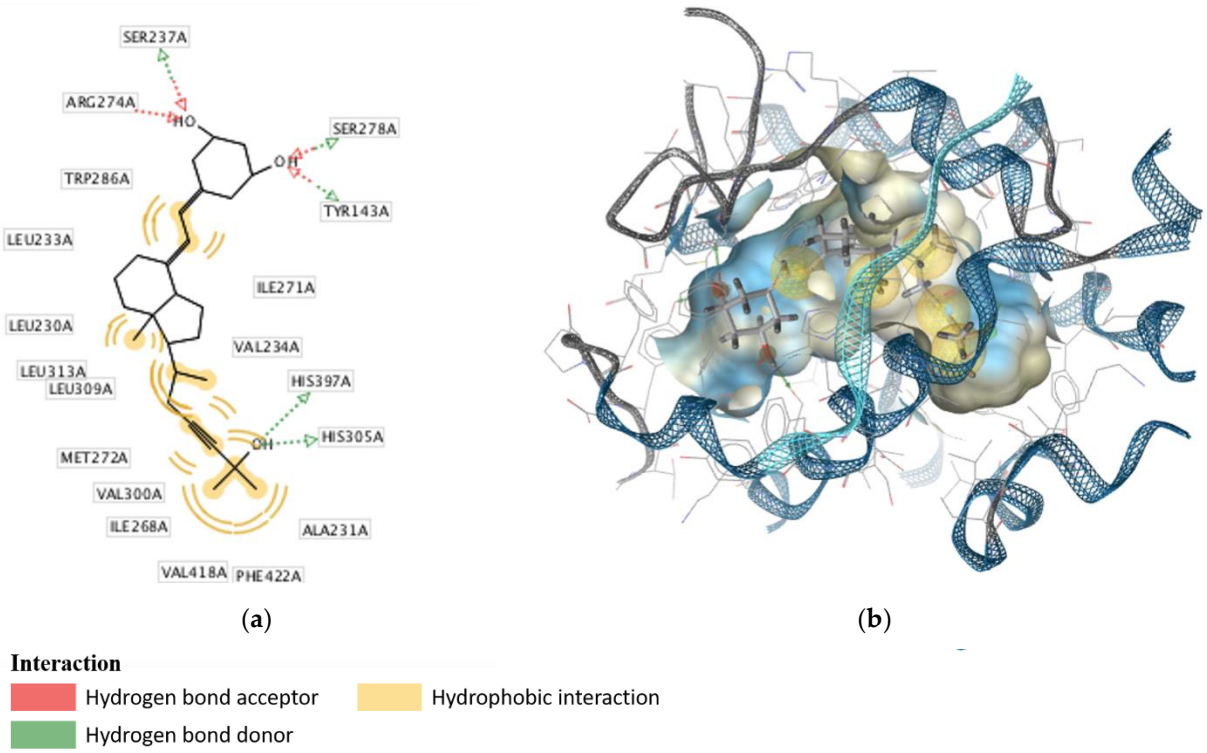

Figure 1. (a) Detail bonding of molecular interaction between TX5 and 1TXI in 2D visualization, (b) The 3D interaction of TX5 at the binding pocket of 1TXI.

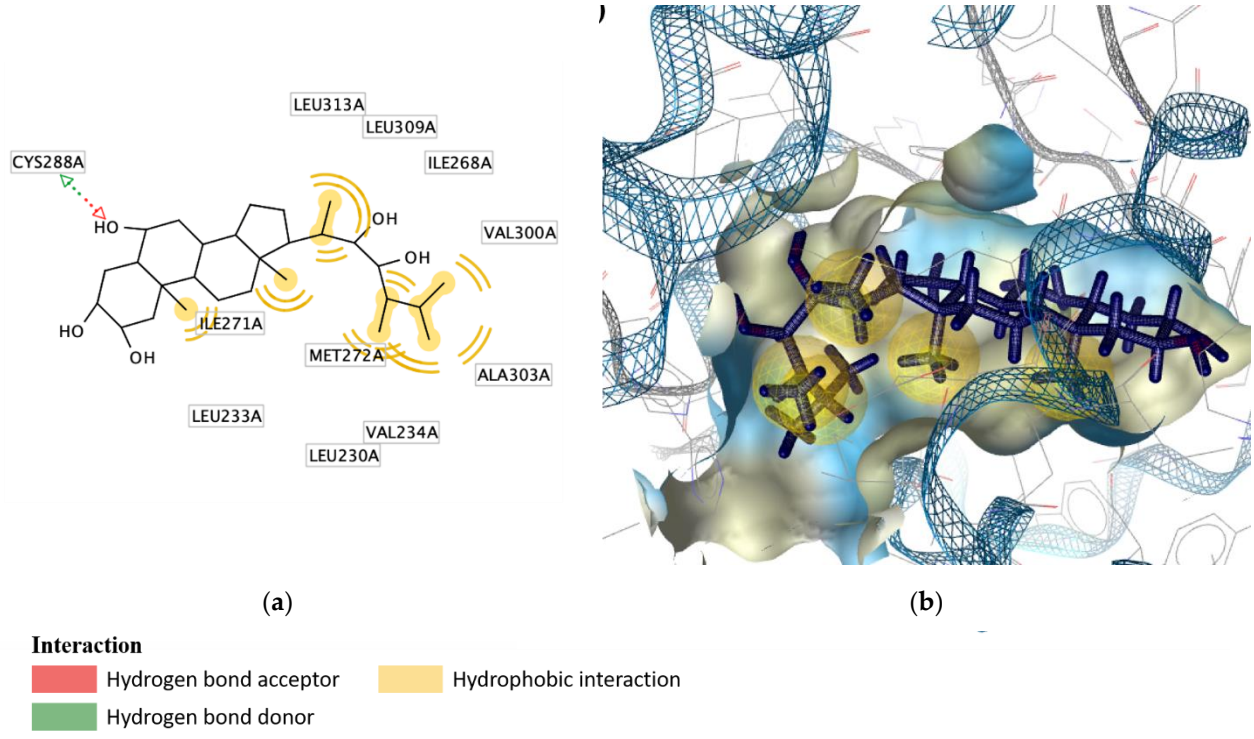

Figure 2. (a) Detail bonding of molecular interaction between dolichosterone and 1TXI in 2D visualization, (b) The 3D interaction of dolichosterone the binding pocket of 1TXI.

This study used Vitamin D receptor (PDB ID: 1TXI) as a potential protein target for inducing a similar response as Vitamin D3 does to generate various gene expressions depending on the target cell. In this case, we expect the possible ligand candidate can prevent hair loss in menopausal women as one of the consequences of decreased calcium and Vitamin D level in their bodies. The potential ligands used in this study based on the pharmacophore feature similarity are Dolichosterone, Gartanin, (-)-Matairesinol, Luteolin, Glucobrassin, 5-HETE, 9-ribosyl-cis-zeatin, Sinapyl glucoside, 9-ribosyl-trans-zeatin, and geraniol.

In this study, we have done molecular docking study of Inecalcitol (PDB ID: TX5) as our positive control. Inecalcitol is an analog of 1,25-dihydroxyvitamin D3 or calcitriol, widely known as the active form of Vitamin D in the human body.[14] Calcitriol itself have a role in regulating the population of keratinocytes stem cells in the bulge region of hair follicles by binding to Vitamin D receptor in the cell nucleus. Lower vitamin D or defective vitamin D receptor was associated with disruption of keratinocytes stem cells renewal, leading to female pattern hair loss due to incomplete hair follicle cycle.[6] Calcitriol supplementation is widely used to treat calcium deficiency caused by hypoparathyroidism and metabolic bone disease caused by chronic kidney disease. However, this supplementation also can cure hair loss in a woman with Vitamin D deficiency in her serum based on the case report by Suad and Modawe (2018).[15]

Our docking between VDR and ligands using Autodock version 4.2 showed the binding energy of the possible ligand candidates ranging from -9.72 to 4.96 kcal/mol. Dolichosterone is the compound with the lowest binding energy among the chosen compounds. Meanwhile, Inecalcitrol as positive control has a binding energy of -13.02 kcal/mol.

Dolichosterone is an organic compound from the tetrahydroxy bile acid class, while (-)-Matairesinol is classified as phenylpropanoid. Dolichosterone and (-)-Matairesinolcan be extracted from Poaceae (grains) and Fabaceae (legumes) family plants. Classified as a steroid compound and possibly the closest compound to calcitriol structure, Dolichosterone may metabolize in steroid pathway or as energy storage in the human body. Dolichosterone, popularly extracted from hyacinth bean, that known to have antioxidant, anticancer, and hepatoprotective effects.[16] (-)-Matairesinol is the compound that carries grains that benefit cardiovascular health.[17]

Gartanin is one of the famous extracted compounds from mangosteen fruit (*Garcinia mangostana*). Gartanin is well known for its anti-inflammation, antioxidant, antifungal, and anticancer effects. Gartanin also has a neuroprotective role by suppressing oxidative stress caused by glutamate. In study conducted by Li, et al. in 2016, gartanin have a degrading effect on androgen receptor, that play a role in hair loss in menopausal women.[18–21]

5-Hydroxyeicosatetraenoic acid (5-HETE) is one of the arachidonic acid metabolites. 5-HETE is one of the intermediate compounds in the leukotriene synthesis pathway and acts as a biomarker in evaluating eicosanoid metabolism in the pathologic process. In terms of functionality in plants, the arachidonic acid system is homologous with the oxylipins system. The Oxylipin system was first found in soybean extract and further researched in Arabidopsis thaliana.[22,23]

Sinapyl glucoside is one of the compounds extracted from *Magnolia sieboldii* from East Asia. The hydrolyzed version of this compound is known for its anti-inflammatory and anti-nociceptive character.[24]

Geraniol is one of the monoterpene compounds easily extracted from any part of plants, such as leaves, fruits, stems, and flowers. Geraniol is mostly found in plants with aromatic scents, such as roses, lavender, and lemongrass. Geraniol has antimicrobials, anti-inflammatory, antioxidant, anticancer, and neuroprotective character.[25]

Binding energy data from docking results showed that Dolichosterone, Gartanin, (-)-Matairesinol, 5-HETE, Sinapyl glucoside, and Geraniol, are compounds that may extracted from herbal plants for the next studies. Thus, we recommended to be researched as the possible agonist of VDR in further in vitro and in vivo studies.

4. Materials and Methods

4.1. Protein receptors preparation

The three-dimension structure of the VDR (PDB ID: 1TXI) (Figure 3) was retrieved from the Protein Data Bank (https://rcsb.org/) in the format of .pdb.[10] Then, the protein was refined by removing water molecules, removing unnecessary chains, and adding polar hydrogen and charges using Autodock version 4.2. The processed protein structure was then saved in .pdb format for further analysis.

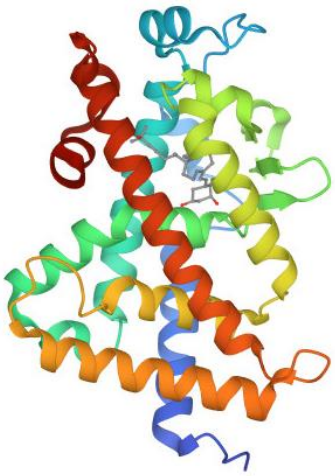

Figure 3. 3D structure of vitamin D receptor (VDR) (PDB ID: 1TXI).[10]

4.2 Pharmacopore modelling and possible ligand candidate screening

Processed protein from the latest step was processed to identify the pharmacophore binding site and screen possible ligand candidate screening with LigandScout version 4.4.[11] After placing the pharmacophore binding site, possible ligand candidate screening was performed using HerbalDB Database.[12] Because there is no exact potential ligand to all pharmacophore has found, the screening then adjusted to omit no more than half of the identified pharmacophore binding site. Ten highest pharmacophore-fit scores of the possible ligand candidates were chosen to be processed in the next step.

4.3. Ligand preparation and drug-likeness activity

Three-dimension structure of Inecalcitol, Vitamin D analog (PDB ID: TX5) as native ligand of VDR (Figure 4a) and 10 choosen possible ligand candidate was retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Figure 2b-2k) in .sdf format, then cleaned to form 3D visualization and converting them into .pdb format using MarvinSketch

The drug-likeness analysis was performed with SWISSADME (https://swissadme.ch/) to assess every qualitatively the possibility of a molecule to become an oral drug by respecting some factors, such as bioavailability. Lipinski's Rule of Five was used as guide to assess good permation and oral absorption properties, i.e., molecular weight less than 500 Da, C logP <5, hydrogen bond donor <5, hydrogen acceptor <10, violation <2.[13]

4.4. Molecular docking

The device used in this study is a personal computer (PC) with Intel Core i5-7200U CPU @2.50-2.71GHz, 8GB RAM. Operating System used was Windows 10, 64-bit OS. First, molecular docking was processed with the native ligand of the protein to validate the consistency of the molecular docking process with root mean square deviation (RMSD) value below 2 Å. The grid coordinate (X, Y, Z) -10.502, 22.258, 34.073 with Grid Box dimension 40x40x40. Through the docking process, the macromolecule was kept rigid, and the ligand was flexible. The molecular docking was performed using Autodock version 4.2 by adjusting the parameter of the genetic algorithm (GA), using ten runs of the criteria of Lamarckian GA. Vitamin D receptor (PDB ID: 1TXI) was docked with ten molecules and one native ligand and explored using Autodock version 4.2

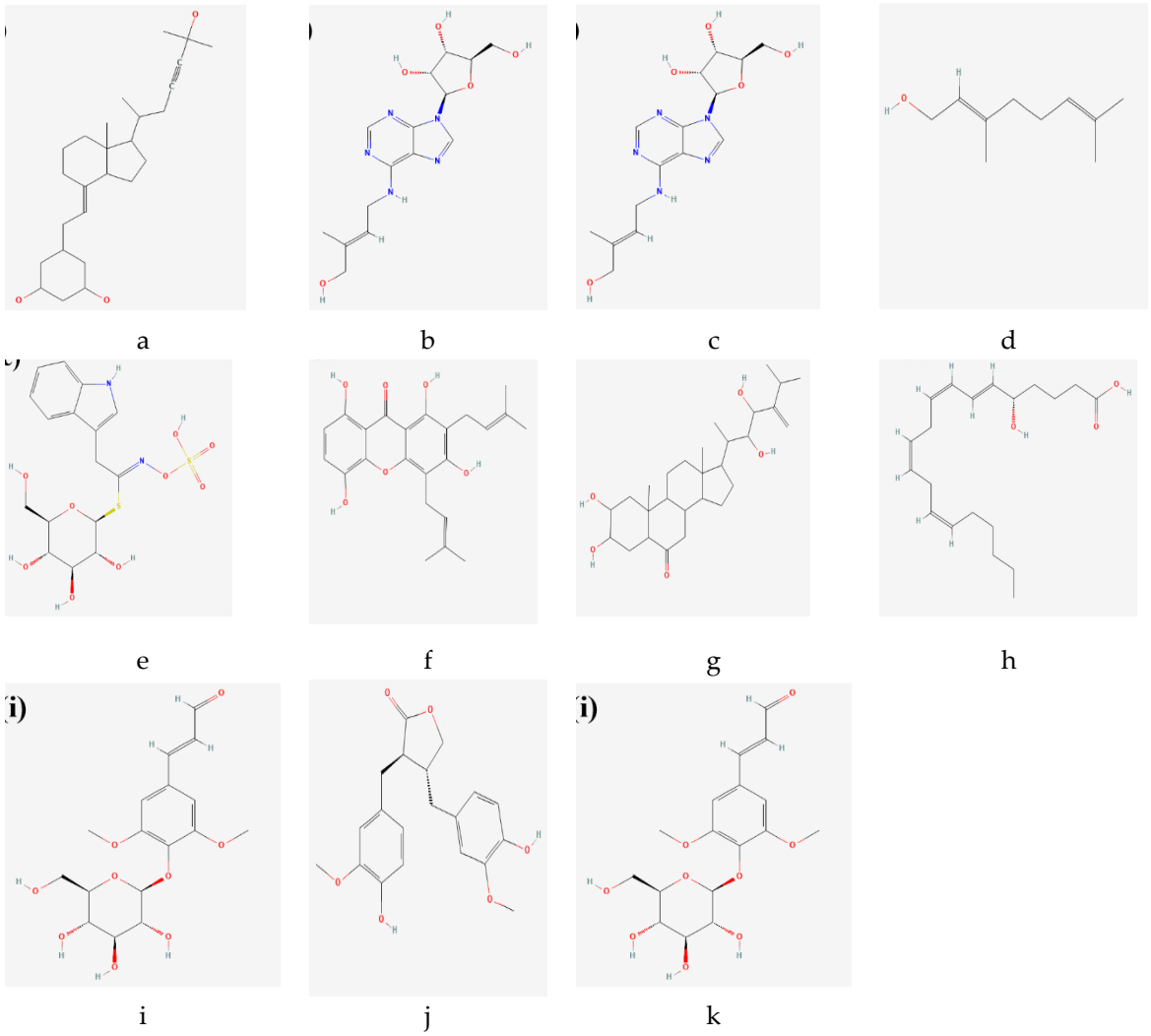

Figure 4. 2D structure of (a) vitamin D analog, TX5; (b) 9-ribosyl-trans-zeatin; (c) luteolin; (d) geraniol; (e) glucobrassicin; (f) gartanin; (g) dolichosterone; (h) 5-HETE; (i) sinapyl glucoside; (j) (-)-mataresinol; and (k) 9-ribosyl-cis-zeatin.

5. Conclusions

Hair loss is commonly found among menopausal women. Although it is also well-known that hormonal dynamics mainly cause hair loss, developing countries such as Indonesia are more open to herbal-based therapeutics instead of synthetical-based therapeutics. Thus, herbal-derived compounds may become an alternative to activate VDR as calcitriol does as a native ligand. From docking results and drug-likeness parameter, Dolichosterone, Gartanin, and (-)-Matairesinol, Luteolin, 5-HETE, Sinapyl glucoside, and geraniol showed preliminary potency as vitamin D receptor agonist. However, the binding energy of native ligand toward VDR still much higher than the experimented possible ligands. Nevertheless, more research is required to determine each compound drug potential and maximize compound extraction from the medicinal plant to achieve therapeutic concentration for medicinal purposes.

6. Patents

Conflicts of Interest: We want thanks to bioinformatics elective modules team, Medical Chemistry Department, Faculty Medicine, Universitas Indonesia for the guidance in manuscript writing and data interpretation. The corresponding author had the responsibility for the decision for publication.

References

1. Goluch-Koniuszy ZS. Nutrition of women with hair loss problem during the period of menopause. Przegląd Menopauzalny Menopause Rev. 2016 Mar;15(1):56–61.
2. Tosti A, Piraccini BM, Iorizzo M, Misciali C. Frontal fibrosing alopecia in postmenopausal women. J Am Acad Dermatol. 2005 Jan;52(1):55–60.
3. Chaikittisilpa S, Rattanasirisin N, Panchaprateep R, Orprayoon N, Phutrakul P, Suwan A, et al. Prevalence of female pattern hair loss in postmenopausal women: a cross-sectional study. Menopause. 2022 Apr;29(4):415–20.
4. Sattar F, Almas U, Ibrahim NA, Akhtar A, Shazad MK, Akram S, et al. Efficacy of Oral Vitamin D3 Therapy in Patients Suffering from Diffuse Hair Loss (Telogen Effluvium). J Nutr Sci Vitaminol (Tokyo). 2021;67(1):68–71.
5. Yadav DK, Kumar S, Teli MK, Kim MH. Ligand-based pharmacophore modeling and docking studies on vitamin D receptor inhibitors. J Cell Biochem. 2020;121(7):3570–83.
6. Banihashemi M, Nahidi Y, Meibodi NT, Jarahi L, Dolatkhah M. Serum Vitamin D3 Level in Patients with Female Pattern Hair Loss. Int J Trichology. 2016;8(3):116–20.
7. Kusmana C, Hikmat A. The Biodiversity of Flora in Indonesia. J Nat Resour Environ Manag. 2015 Dec 1;5:187–98.
8. Welz AN, Emberger-Klein A, Menrad K. Why people use herbal medicine: insights from a focus-group study in Germany. BMC Complement Altern Med. 2018 Mar 15;18(1):92.
9. van Andel T, Carvalheiro LG. Why Urban Citizens in Developing Countries Use Traditional Medicines: The Case of Suriname. Evid Based Complement Alternat Med. 2013 Apr 7;2013:e687197.
10. Huang YH, Rose PW, Hsu CN. Citing a Data Repository: A Case Study of the Protein Data Bank. PLOS ONE. 2015 Aug 28;10(8):e0136631.
11. Wolber G, Langer T. LigandScout: 3-D Pharmacophores Derived from Protein-Bound Ligands and Their Use as Virtual Screening Filters. J Chem Inf Model. 2005 Jan 1;45(1):160–9.
12. Yanuar A, Mun'im A, Lagho A, Syahdi RR, Rahmat M, Suhartanto H. Medicinal Plants Database and Three Dimensional Structure of the Chemical Compounds from Medicinal Plants in Indonesia. Int J Comput Sci. 2011 Nov 28;8.
13. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001 Mar 1;46(1–3):3–26.
14. Eelen G, Verlinden L, Rochel N, Claessens F, De Clercq P, Vandewalle M, et al. Superagonistic Action of 14-epi-Analogs of 1,25-Dihydroxyvitamin D Explained by Vitamin D Receptor-Coactivator Interaction. Mol Pharmacol. 2005 May;67(5):1566–73.
15. Suad HH, Modawe GA. Investigation of Diffuse Hair Fall Case Due to Vitamin D Deficiency: A Case Report and Literature Review. Sudan J Med Sci SJMS. 2018 Jun 28;91–7.
16. Seo CS. Determination of the marker compound, chikusetsusaponin IVa in Dolichos lablab L. using HPLC–PDA and HPLC–ELSD. South Afr J Bot. 2020 May 1;130:471–4.
17. Piironen V, Lampi AM, Ekholm P, Salmenkallio-Marttila M, Liukkonen KH. Micronutrients and phytochemicals in wheat grain. Wheat Chem Technol. 2009 Jan 1;179–222.
18. Rukthong P, Sereesongsang N, Kulsirirat T, Boonnak N, Sathirakul K. In vitro investigation of metabolic fate of α-mangostin and gartanin via skin permeation by LC-MS/MS and in silico evaluation of the metabolites by ADMET predictorTM. BMC Complement Med Ther. 2020 Nov 23;20(1):359.
19. Gao XY, Wang SN, Yang XH, Lan WJ, Chen ZW, Chen JK, et al. Gartanin Protects Neurons against Glutamate-Induced Cell Death in HT22 Cells: Independence of Nrf-2 but Involvement of HO-1 and AMPK. Neurochem Res. 2016 Sep;41(9):2267–77.
20. Li G, Petiwala SM, Yan M, Won JH, Petukhov PA, Johnson JJ. Gartanin, an isoprenylated xanthone from the mangosteen fruit (Garcinia mangostana), is an androgen receptor degradation enhancer. Mol Nutr Food Res. 2016 Jun;60(6):1458–69.
21. de Mello RFA, de Souza Pinheiro WB, Benjamim JKF, de Siqueira FC, Chisté RC, Santos AS. A fast and efficient preparative method for separation and purification of main bioactive xanthones from the waste of Garcinia mangostana L. by high-speed countercurrent chromatography. Arab J Chem. 2021 Aug 1;14(8):103252.
22. Wilson JF. 5-Hete. In: Wilson JF, editor. Drugs Eicosanoids: Second Messengers November 1995 [Internet]. Dordrecht: Springer Netherlands; 1995 [cited 2022 Jan 3]. p. 1768–1768. (Immunoassay Kit Directory). Available from: https://doi.org/10.1007/978-94-011-0679-5_77
23. Griffiths G. Biosynthesis and analysis of plant oxylipins. Free Radic Res. 2015 May 4;49(5):565–82.
24. Choi J, Shin KM, Park HJ, Jung HJ, Kim HJ, Lee YS, et al. Anti-inflammatory and antinociceptive effects of sinapyl alcohol and its glucoside syringin. Planta Med. 2004 Nov;70(11):1027–32.
25. Madan Kumar A, T Devaki. Geraniol, a component of plant essential oils: a review of its pharmacological activities. Int J Pharm Pharm Sci. 2015 Apr 1;67–70.