STUDI *IN SILICO*: POTENSI DAN MEKANISME SENYAWA AKTIF BIJI KACANG TUNGGAK (*Vigna unguiculata*) SEBAGAI ANTIDISLIPIDEMIA MELALUI INHIBISI HMG-CoA REDUKTASE DAN AKTIVASI RESEPTOR LDL

SKRIPSI

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RINGKASAN

Gistha Putri Pinasthika. Fakultas Kedokteran, Universitas Islam Malang, Januari 2023. Studi *in silico*: Potensi dan Mekanisme Senyawa Aktif Biji Kacang Tunggak (*Vigna unguiculata*) Sebagai Antidislipidemia Melalui Inhibisi HMG-CoA Reduktase dan Aktivasi Reseptor LDL. **Pembimbing 1:** Dr. dr. Dini Sri Damayanti, M.Kes. **Pembimbing 2:** dr. H. R. Muh. Hardadi Airlangga, Sp.PD

Pendahuluan: Biji *Vigna unguiculata* berpotensi untuk mempengaruhi profil lipid, tetapi mekanisme kerjanya belum diketahui secara pasti sehingga membuka peluang untuk diuji secara in silico. Inhibisi 3-*Hydroxy-3-Methylglutaryl Coenzyme A Reductase* (HMGCR) dapat menurunkan sintesis kolesterol di hepar yang menurunkan sintesis VLDL sehingga meningkatkan HDL. Aktivasi *Low Density Lipoprotein* (LDLR) meningkatkan ambilan LDL sirkulasi menyebabkan LDL di sirkulasi menurun. LDL dibawa masuk ke hepar menjadi garam empedu untuk diekskresikan melalui feses. Studi ini bertujuan mengetahui mekanisme senyawa aktif biji *Vigna unguiculata* untuk menginhibisi HMGCR dan aktivasi LDLR sekaligus memprediksi kemampuan senyawa sebagai kandidat obat oral.

Metode: Metode komputasi *in silico* menggunakan software berbasis web Docking Server. Senyawa aktif biji *Vigna unguiculata* ditambatkan HMGCR (ID: 1DQA) dan LDLR (ID: 1AJJ) dengan simvastatin sebagai pembanding. Evaluasi berdasarkan ΔG, Ki, interaksi permukaan, dan residu asam amino. Uji fisikokimia (*Lipinski's's rule of five)*, uji farmakokinetik (ADME), dan toksisitas (LD50).

Hasil: Afinitas senyawa berdasarkan -ΔG dan residu asam amino, semakin rendah -ΔG maka semakin kecil energi yang dibutuhkan untuk berikatan dengan protein target. Semakin tinggi kesamaan residu asam amino senyawa dibanding simvastatin, maka senyawa mempunyai kesamaan aktivitas untuk menghambat HMGCR dan aktivasi LDLR. Hasil penambatan HMGCR simvastatin (-8,00kcal/mol, 100%); cycloartenol (-9,7kcal/mol, 87%); stigmasterol (-8,75kcal/mol, 50%); genistin (-7kcal/mol, 25%). Hasil penambatan LDLR simvastatin (6,29kcal/mol, 100%); cycloartenol (-7,30kcal/mol, 83%); stigmasterol (-7,10kcal/mol, 100%); genistin (-6,75kcal/mol, 50%); daidzin (-6,58 kcal/mol, 66%). Sifat fisikokimia senyawa dengan hasil penambatan terbaik memenuhi 3 dari 4 kriteria kecuali daidzin terpenuhi 4 dari 4 kriteria. Sehingga cycloartenol, stigmasterol, daidzin, dan genistin termasuk memenuhi aturan Lipinski. Sifat farmakokinetik senyawa cycloartenol dan stigmasterol masing-masing memenuhi 5 dari 8 kriteria dengan absorbsi paling tinggi, tidak mengaktivasi CYP3A4 inhibitor sehingga penggunaan dosis tinggi tidak toksik, dan tidak bersifat toksik berdasarkan LD50.

Kesimpulan: Senyawa cycloartenol dan stigmasterol memiliki hasil penambatan terbaik terhadap HMGCR dan LDLR, mudah larut, dan tidak toksik pada penggunaan dosis tinggi, dan aman dikonsumsi berdasarkan LD50.

Kata kunci: *Vigna unguiculata; Anti-Dislipidemia; Simvastatin; In silico*

SUMMARY

Gistha Putri Pinasthika. Faculty of Medicine, Islamic University of Malang, January 2023. In silico Studies: Potency and Mechanism of Active Compounds of Delinquent Bean Seeds (Vigna unguiculata) As AntiDislipidemia Through HMG-CoA Reductase Inhibition and LDL Receptor Activation. **Supervisor 1:** Dr. dr. Dini Sri Damayanti, M.Kes**. Supervisor 2:** dr. H. R. Muh. Hardadi Airlangga, Sp.PD

Introduction: : The seeds of Vigna unguiculata have the potential to affect the lipid profile, but the mechanism of action is not yet known for certain so it opens up the opportunity to be tested in silico. Inhibition of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase (HMGCR) can lower cholesterol synthesis in liver which affects VLDL synthesis thereby increasing HDL. Activation of Low Density Lipoprotein (LDLR) expression increases the uptake of circulating LDL causing LDL in the circulation to decrease. LDL is carried into the liver into bile salts to be excreted through feces. This study aims to determine the mechanism of the active compound of Vigna unguiculata seeds to inhibit HMGCR and LDLR activation while predicting the compound's ability as an oral drug candidate.

Method: The in silico computing method uses web-based software Docking Server. The active compounds of *Vigna unguiculata* seeds were docking to HMGCR (ID: 1DQA) and LDLR (ID: 1AJJ) with simvastatin as a comparison. Evaluation based on ΔG, Ki, surface interaction, and amino acid residues. Physicochemical assay (Lipinski's rule of five), pharmacokinetic test (ADME), and toxicity (LD50).

Results: The affinity of compounds based on $-\Delta G$ and amino acid residues, the lower $-\Delta G$, the smaller the energy required to bind to the target protein. The higher the similarity of amino acid residues of compounds compared to simvastatin, the compounds have similar activities to inhibit HMGCR and LDLR activation. HMGCR simvastatin tethering results (-8.00kcal/mol, 100%); cycloartenol (-9.7kcal/mol, 87%); stigmasterol (-8.75kcal/mol, 50%); genistin (-7kcal/mol, 25%). LDLR simvastatin tethering results (6.29kcal/mol, 100%); cycloartenol (-7.30kcal/mol, 83%); stigmasterol (-7.10kcal/mol, 100%); genistin (-6.75kcal/mol, 50%); daidzin (-6.58 kcal/mol, 66%). The physicochemical properties of compounds with the best tethering results meet 3 of the 4 criteria unless the daidzin meets 4 of the 4 criteria. So cycloartenol, stigmasterol, daidzin, and genistin are included in Lipinski's rule. The pharmacokinetic cycloartenol and stigmasterol, each met 5 of the 8 criteria with the highest absorption, did not activate CYP3A4 inhibitors so that the use of high doses was not toxic, and was not toxic based on LD50.

Conclusion: Cycloartenol and stigmasterol compounds have the best tethering results against HMGCR and LDLR, are easily soluble, and are non-toxic at high doses of use, and are safe to take based on LD50.

Keywords: *Vigna unguiculata; Anti-Dyslipidemia; Simvastatin; In silico*

BAB I
PENDAHULUAN

1.1 Latar Belakang

Dislipidemia adalah penyakit yang terjadi akibat ketidakseimbangan kolesterol total, *Low Density Lipoprotein* (LDL), Trigliserida (TG), dan *High Density Lipoprotein* (HDL) (Obsa et al., 2022). Dislipidemia merupakan faktor resiko utama aterosklerosis, menjadi penyebab penyakit kardiovaskular dan di Indonesia insidensi tiap tahunnya terus meningkat (Rahmawati & Dewi Sartika, 2020). Faktor resiko dislipidemia adalah kurang aktivitas fisik dan diet tinggi lemak yang menimbulkan hipertrofi adiposa sehingga menginduksi resisten insulin dan lipolisis pada adiposa. Hal ini dapat meningkatkan *Free Faty Acid* (FFA) plasma yang masuk ke hepar (Ipsen et al., 2016). FFA di hepar membentuk *Very Low-Density Lipoprotein* (VLDL) yang dikeluarkan ke sirkulasi (Ipsen et al., 2016). Peningkatan VLDL plasma meningkatkan aktivitas *Cholesteryl Ester Transfer Protein* (CETP), sehingga terjadi peningkatan pertukaran TG-VLDL terhadap *Cholesteryl Ester - High Density Lipoprotein* (CE-HDL) dan *Low Density Lipoprotein* (LDL) (González-Lleó et al., 2022). Hal ini menyebabkan penurunan HDL karena mudah dikatabolisme dan peningkatan LDL yang pro-aterogenik (Klop et al., 2013).

Penatalaksanaan dislipidemia dapat dilakukan dengan pemberian beberapa obat yaitu statin, fibrat, niasin, ezetimebe, dan bile acid sequestrants (Mach et al., 2020). Namun pemberian obat ini diketahui dapat memberikan efek samping, dijumpai 8% pasien di rumah sakit Amerika Serikat disebabkan efek samping obat

dan tiap tahun ribuan orang meninggal karena obat bebas yang dianggap aman (Karimi et al., 2015). Kejadian ini membuat masyarakat memilih kembali pada herbal, yang dipercaya hampir tidak menimbulkan efek samping, mudah didapat, dan murah (Jennifer & Saptutyningsih, 2015). Konsumsi kacang dikaitkan dengan penurunan risiko penyakit jantung koroner (Frota et al., 2015). Dalam studi epidemiologi observasional terbukti konsumsi kacang dapat menurunkan kolesterol total dan LDL dalam uji klinis, tetapi sebagian besar peneliti hanya meneliti kacang kedelai dibandingkan jenis kacang lainnya (Frota et al., 2015). Sedangkan penelitian lain membuktikan biji kacang tunggak (*Vigna unguiculata*) memberikan efek perlindungan terhadap beberapa penyakit kronis seperti penyakit kardiovaskular, hiperkolesterolemia, dan obesitas (Carneiro da Silva et al., 2021).

Biji kacang tunggak memiliki efek farmakologi sebagai hipokolesterolemia, antihiperglikemia, antioksidan, dan antibakteri (Sayeed et al., 2017). Penelitian in vivo pada tikus dengan diet tinggi kolesterol dan biji kacang tunggak terbukti menurunkan total kolesterol, TG, LDL, dan meningkatkan HDL (Allah et al., 2017). Uji fitokimia pada biji kacang tunggak menunjukkan kandungan alkaloid, flavonoid, saponin, sterol, fenolik (Igboabuchi, 2021). Melalui *Prediction of Activity Spectra of Substances* (PASS) menunjukkan senyawa aktif biji kacang tunggak memiliki aktivitas farmakologi sebagai *Cholesterol antagonist* dan *Antihypercholesterolemic.* Dengan nilai Pa >0,6, maka senyawa biji kacang tunggak memiliki aktivitas farmakologi eksperimental. Penelitian yang ada belum banyak meneliti potensi biji kacang tunggak untuk mencegah dislipidemia melalui studi *in silico*.

Studi *in silico* merupakan metode komputasi sebagai jalan pintas virtual yang membantu penelitian lebih cepat, hemat biaya, dan mengurangi pemakaian alat dan bahan yang berlebihan (Dona et al., 2019). In silico bertujuan untuk menganalisis interaksi senyawa aktif terhadap protein target (Suryani, 2018). Metode in silico dapat memprediksi mekanisme senyawa aktif biji kacang tunggak sebagai inhibitor HMGCR dan aktivasi LDLR dengan simvastatin sebagai pembanding karena memiliki mekanisme kerja yang sama. Peran HMGCR sebagai kontrol utama pembatas kecepatan sintesis kolesterol endogen dan LDLR dapat mengikat LDL plasma untuk diangkut ke hepar. Jika HMGCR diinhibisi dan LDLR diaktivasi, selain penurunan kolesterol juga menurunkan VLDL dan peningkatan HDL. Potensi senyawa aktif kacang tunggak sebagai obat oral yang aman, dapat diketahui dari uji sifat fisikokimia (*Lipinski's rule of five*), sifat farmakokinetik, dan toksisitas (Maftucha et al., 2022).

1.2 Rumusan Masalah

1. Bagaimana afinitas dari penambatan senyawa aktif biji kacang tunggak (*Vigna unguiculata*) terhadap HMGCR di hepar secara in silico?

2. Bagaimana afinitas dari penambatan senyawa aktif biji kacang tunggak (*Vigna unguiculata*) terhadap LDLR di hepar secara in silico?

3. Bagaimana sifat fisikokimia senyawa aktif biji kacang tunggak (*Vigna unguiculata*) berdasarkan *Lipinski's rule of five* pada pkCSM *online tool*?

4. Bagaimana sifat farmakokinetik absorbsi, distribusi, metabolisme, dan ekskresi senyawa aktif biji kacang tunggak (*Vigna unguiculata*) pada pkCSM *online tool*?

5. Bagaimana toksisitas senyawa aktif biji kacang tunggak (*Vigna unguiculata*) berdasarkan LD50 pada pkCSM *online tool*?

1.3 Tujuan Penelitian

1. Mengetahui afinitas dari penambatan senyawa aktif biji kacang tunggak (*Vigna unguiculata*) terhadap HMGCR di hepar secara *in silico*.

2. Mengetahui afinitas dari penambatan senyawa aktif biji kacang tunggak (*Vigna unguiculata*) terhadap LDLR di hepar secara *in silico*.

3. Mengetahui sifat fisikokimia senyawa aktif biji kacang tunggak (*Vigna unguiculata*) berdasarkan *Lipinski's rule of five* pada pkCSM *online tool*.

4. Mengetahui sifat farmakokinetik absorbsi, distribusi, metabolisme, dan ekskresi senyawa aktif biji kacang tunggak (*Vigna unguiculata*) pada pkCSM *online tool*.

5. Mengetahui toksisitas senyawa aktif biji kacang tunggak (*Vigna unguiculata*) berdasarkan LD50 pada pkCSM *online tool*.

1.4 Manfaat Penelitian

1.4.1 Manfaat Teoritis

Penelitian ini diharapkan dapat menjadi dasar ilmiah dalam penelitian lebih lanjut potensi dan mekanisme biji kacang tunggak untuk mencegah dislipidemia.

1.4.2 Manfaat Praktisi

Sebagai pilihan alternatif dalam tatalaksana farmakologi untuk mencegah dislipidemia.

BAB VII
KESIMPULAN DAN SARAN

7.1 Kesimpulan

1. Senyawa aktif biji kacang tunggak memiliki afinitas tinggi terhadap HMGCR diantaranya cycloartenol dan stigmasterol, yang mempunyai ikatan kuat dan mampu menghambat HMGCR dengan baik dibanding simvastatin, sedangkan genistin lebih rendah dari simvastatin.

2. Senyawa aktif biji kacang tunggak mempunyai afinitas tinggi terhadap LDLR yaitu cycloartenol, stigmasterol, daidzin, dan genistin. Ikatan yang terbentuk lebih kuat terhadap LDLR dibanding simvastatin.

3. Sifat fisikokimia senyawa cycloartenol, stigmasterol, daidzin, dan genistin memenuhi kriteria Lipinski sehingga senyawa mudah larut.

4. Sifat farmakokinetik senyawa cycloartenol dan stigmasterol memiliki absorbsi tinggi dan tidak mengaktifkan CYP2D6/CYP3A4 inhibitor sehingga tidak bersifat toksik.

5. Uji toksisitas berdasarkan LD50 cycloartenol, stigmasterol, genistin, dan daidzin aman dikonsumsi.

7.2 Saran

Berdasarkan hasil yang diperoleh dari penelitian ini, maka untuk mengembangkan lebih lanjut dapat dilakukan:

1. Penelitian in silico selanjutnya dapat menggunakan sumber organisme hewan seperti tikus atau mencit.

2. Penelitian lanjutan mengenai potensi senyawa aktif biji kacang tunggak sebagai antidislipidemia melalui studi in vivo untuk membuktikan potensi senyawa aktif biji kacang tunggak dapat menghambat HMGCR dan meningkatkan LDLR.

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