SKRIPSI

MOLECULAR DOCKING SENYAWA BIOAKTIF EMODIN TERHADAP RESEPTOR VEGF PADA KANKER SERVIKS

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FAKULTAS KEDOKTERAN

UNIVERSITAS SRIWIJAYA

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Diajukan untuk memenuhi salah satu syarat guna memperoleh gelar
Sarjana Kedokteran (S.Ked)

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HALAMAN PENGESAHAN

***MOLECULAR DOCKING* SENYAWA BIOAKTIF EMODIN TERHADAP RESEPTOR VEGF PADA KANKER SERVIKS**

LAPORAN AKHIR SKRIPSI

Diajukan Untuk Melengkapi Salah Satu Syarat Memperoleh
Gelar Serjana Kedokteran (S.Ked)

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Karya tulis ilmiah berupa Skripsi ini dengan judul " *Molecular Docking* Senyawa Bioaktif Emodin Terhadap Reseptor VEGF Pada Kanker Serviks" telah dipertahankan di hadapan Tim Penguji Karya Tulis Ilmiah Program Studi Pendidikan Dokter Umum Fakultas Kedokteran Universitas Sriwijaya pada tanggal 02 Desember 2024

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Menyatakan bahwa skripsi saya merupakan hasil karya sendiri didampingi tim pembimbing dan bukan hasil penjiplakan/plagiat. Apabila ditemukan unsur penjiplakan/plagiat dalam skripsi ini, maka saya bersedia menerima sanksi akademik dari Universitas Sriwijaya sesuai aturan yang berlaku.

Demikian, pernyataan ini saya buat dalam keadaan sadar dan tanpa ada paksaan dari siapapun.

Palembang, 02 Desember 2024

Innayah Rania Farzana

ABSTRAK

MOLECULAR DOCKING SENYAWA BIOAKTIF EMODIN TERHADAP RESEPTOR VEGF PADA KANKER SERVIKS

(Innayah Rania Farzana, 02 Desember 2024, 81 Halaman)
Fakultas Kedokteran, Universitas Sriwijaya

Kanker serviks merupakan salah satu penyebab utama kematian akibat kanker pada perempuan dan menjadi kanker terbanyak ketiga di dunia. Ekspresi VEGF yang tinggi pada kanker serviks dikaitkan dengan prognosis yang buruk, sehingga terapi anti-VEGF mempunyai peran penting dalam penyembuhan kanker serviks. Hasil beberapa penelitian menunjukkan emodin menghambat proliferasi, migrasi, dan pembentukan sel endotel yang distimulasi oleh VEGF. Penelitian ini bertujuan untuk mengetahui interaksi dari senyawa bioaktif emodin terhadap reseptor VEGF pada kanker serviks secara in silico dengan molecular docking. Molecular docking dilakukan dengan beberapa tahapan mulai dari preparasi struktur senyawa bioaktif, preparasi struktur protein target, validasi metode molecular docking, dan docking senyawa bioaktif pada protein target. Nilai energi ikatan yang semakin rendah antara senyawa bioaktif dan protein target menunjukkan ikatan yang terbentuk semakin kuat dan stabil. Hasil docking menunjukkan nilai pengikatan dari kompleks VEGFR2-emodin sebesar -7,78 kkal/mol dengan tiga ikatan hydrogen dengan asam amino GLU915, CYS917, LEU838 dan tiga van der Waals dengan asam amino PHE916, GLY920, VAL 846. Terdapat interaksi antara senyawa bioaktif emodin dengan VEGFR2 ditandai dengan nilai pengikatan yang baik (-7,78 kkal/mol) serta membentuk ikatan yang stabil ditandai dengan 3 ikatan hidorgen dan 3 interaksi van der waals.

Kata Kunci: *Molecular docking*, emodin, VEGFR2, kanker serviks

ABSTRACT

MOLECULAR DOCKING ON BIOACTIVE COMPOUNDS OF EMODIN TO VEGF RECEPTOR IN CERVIVAL CANCER

(Innayah Rania Farzana, 02 December 2024, 81 Pages)
Faculty of Medicine, Sriwijaya University

Cervical cancer is the main cause of cancer death among woman and the third most cancer case in the world. High expression of VEGF in cervical cancer is linked to a poor prognosis, therefore anti-VEGF therapy has an important role in cervical cancer resolution. Several studies show that emodin inhibit proliferation, migration, and a formation of endothelial cells stimulated by VEGF. This research aims to discover the interaction of the bioactive compound emodin with VEGF receptor in cervical cancer with in silico using molecular docking. Molecular docking involves several steps, starting with the preparation of the bioactive compound structure, preparation of the target protein structure, validation of the molecular docking method, and docking of the bioactive compound to the target protein. A lower binding energy value between the bioactive compound and the target protein indicates that the formed bond is stronger and more stable. The docking results showed the binding energy from VEGFR2-emodin complex is -7.78 kcal/mol with three hydrogen bonds formed with GLU915, CYS917, LEU838 amino acids and three van der Waals formed with PHE916, GLY920, VAL 846 amino acids. There is an interaction between the bioactive compound, emodin and VEGFR2, characterized by a good binding value (-7,78 kkal/mol) and formed a stable binding characterized by 3 hydrogen bonds and 3 van der Waals interactions**.**

Keyword: Molecular docking, emodin, VEGFR2, cervical cancer

RINGKASAN

MOLECULAR DOCKING SENYAWA BIOAKTIF EMODIN TERHADAP RESEPTOR VEGF PADA KANKER SERVIKS

Karya tulis ilmiah berupa skripsi, 2 Desember 2024

Innayah Rania Farzana; Dibimbing oleh Rara Inggarsih, S.S.T., M.Kes dan dr. Ziske Maritska, M.Si.Med

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xviii + 81 halaman, 11 tabel, 21 gambar, 7 lampiran

Kanker serviks adalah salah satu penyebab utama kematian akibat kanker pada perempuan dan menjadi kanker terbanyak ketiga di dunia. Ekspresi VEGF yang tinggi pada kanker serviks dikaitkan dengan prognosis yang buruk, sehingga terapi anti-VEGF mempunyai peran penting dalam penyembuhan kanker serviks. Hasil beberapa penelitian menunjukkan emodin menghambat proliferasi, migrasi, dan pembentukan sel endotel yang distimulasi oleh VEGF. Molecular docking telah menjadi aspek penting dalam pengobatan obat dimana metode ini memprediksi interaksi anatara molekul dan protein pada tingkat atomik. Penelitian ini memiliki tujuan untuk mengetahui interaksi dari senyawa bioaktif emodin terhadap reseptor VEGF pada kanker serviks. Jenis penelitian ini adalah penelitian eksperimental dengan pendekatan secara komputasional. Objek penelitian adalah data sekunder reseptor dan ligan yang diakses dari PDB dan PubChem. Penelitian dilakukan menggunakan laptop pribadi dengan memanfaatkan beberapa laman dan perangkat lunak yang dapat diakses melalui peramban. Hasil docking menunjukkan nilai pengikatan dari kompleks VEGFR2-emodin sebesar -7,78 kkal/mol dengan tiga ikatan hydrogen dengan asam amino GLU915, CYS917, LEU838 dan tiga van der Waals dengan asam amino PHE916, GLY920, VAL 846.
Dapat disimpulkan bahwa terdapat interaksi antara senyawa bioaktif emodin dengan VEGFR2 ditandai dengan nilai pengikatan yang baik (-7,78 kkal/mol) serta membentuk ikatan yang stabil ditandai dengan 3 ikatan hidorgen dan 3 interaksi van der waals.

Kata Kunci: Molecular docking, emodin, VEGFR2, kanker serviks

SUMMARY

MOLECULAR DOCKING SENYAWA BIOAKTIF EMODIN TERHADAP RESEPTOR VEGF PADA KANKER SERVIKS

Scientific Paper in the form of Skripsi, 2 December 2024

Innayah Rania Farzana; Supervised by Rara Inggarsih, S.S.T., M.Kes and dr. Ziske Maritska, M.Si.Med

Medical Science Department, Faculty of Medicine, Sriwijaya University
xviii + 81 pages, 11 tables, 21 pictures, 7 attachments

Cervical cancer is the main cause of cancer death among woman and the third most cancer case in the world. High expression of VEGF in cervical cancer is linked to a poor prognosis, therefore anti-VEGF therapy has an important role in cervical cancer resolution. Several studies show that emodin inhibit proliferation, migration, anda formation of endothelial cells stimulated by VEGF. Molecular docking has become an important aspect in developing drugs where this method predicts interactions between molecules and proteins at the atomic level. This research aims to discover the interaction of the bioactive compound emodin with VEGF receptor in cervical cancer. The type of this research is experimental research with a computational approach. The research object is secondary data of receptors and ligands accessed from PBD and PubChem. The research was done using a personal laptop by utilizing several websites and software that can be accessed with browser. Results: The docking results showed the binding energy from VEGFR2-emodin complex is -7.78 kcal/mol with three hydrogen bonds formed with GLU915, CYS917, LEU838 amino acids and three van der Waals formed with PHE916, GLY920, VAL 846 amino acids.
It can be concluded that there is an interaction between the bioactive compound, emodin and VEGFR2, characterized by a good binding value (-7,78 kkal/mol) and formed a stable binding characterized by 3 hydrogen bonds and 3 van der Waals interactions.

Keywords: Molecular docking, emodin, VEGFR2, cervical cancer

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Memberikan izin kepada Pembimbing dan Universitas Sriwijaya untuk mempublikasikan hasil penelitian saya untuk kepentingan akademik apabila dalam waktu 1 (satu) tahun tidak mempublikasikan karya penelitian saya. Dalam kasus ini saya setuju untuk menempatkan pembimbing sebagai penulis korespodensi (*corresponding author*).

Demikian pernyataan ini saya buat dalam keadaan sadar dan tanpa ada paksaan dari siapapun.

Palembang, 02 Desember 2024

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KATA PENGANTAR

Puji syukur saya ucapkan kehadirat Allah SWT atas rahmat dan karunia-Nya sehingga saya dapat menyelesaikan penyusunan skripsi ini dengan judul "*Molecular Docking* Senyawa Bioaktif Emodin Terhadap Reseptor VEGF pada Kanker Serviks" sebagai salah satu syarat untuk memperoleh gelar Sarjana Kedokteran (S.Ked). Saya menyadari bahwa penyusunan skripsi ini tidak lepas dari bantuan dan dukungan berbagai pihak. Oleh karena itu, saya ingin menghaturkan terima kasih kepada:

1. Allah SWT yang telah memberikan nikmat kesehatan, kelancaran, dan kemudahan dalam semua urusan di hidup saya.
2. Kedua orang tua dan saudara saya yang selalu memberikan doa dan dukungan untuk kemudahan dalam urusan saya.
3. Yang terhormat Ibu Rara Inggarsih, S.S.T., M.Kes dan dr. Ziske Maritska, M.Si.Med selaku pembimbing yang telah memberikan bimbingan, motivasi, ilmu, kritik, dan saran selama penyusunan skripsi ini.
4. Yang terhormat dr. Ayesha Augusta Rosdah, M.Biomed.Sc., PhD dan dr. Soilia Fertila, M.Imun selaku penguji telah memberi masukan dan arahan agar skripsi ini menjadi semakin baik.
5. Teman-teman yang tidak bisa saya sebutkan satu per satu atas segala doa, motivasi, kasih sayang, serta dukungan baik moril maupun materil yang telah diberikan.

Saya menyadari adanya kekurangan dari penelitian ini karena keterbatasan dan kekurangan yang saya miliki. Oleh karena itu, saya terbuka akan kritik dan saran yang bersifat membangun demi perbaikan di masa yang akan datang. Semoga hasil penelitian ini dapat bermanfaat, baik bagi penulis, penelitian selanjutnya, dunia kesehatan, dan lainnya.

Palembang, 2 Desember 2024

Innayah Rania Farzana

DAFTAR ISI

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DAFTAR SINGKATAN

ADMET : *Adsorption, Distribution, Metabolism, Elimination, And Toxicity.*
AIS : *Adenocarcinoma In Situ*
APC : *An Antigen-Presenting Cell*
ASC : *Atypical Squamous Cells*
BCAR4 : *Breast Cancer Anti-Estrogen Resistance 4*
CADD : *Computer Aided Drug Design*
CIN : *Cervical Intraepithelial Neoplasia*
CKD : *Chronic Kidney Disease*
CSC : *Cancer Stem Cells*
CYS : *Cysteine*
DNA : *Deoxyribose Nucleusic Acid*
EBRT : *External Beam Radiation Therapy*
EGFR : *Epidermal Growth Factor Receptor*
ER : *Esterogen Receptor*
ERK : *Extracellular-Signal-Regulated Kinase*
FADD : *Fas-Associated Death Domain*
FAK : *Focal Adhesion Kinase*
FGF : *Fibroblast Growth Factor*
GLU : Asam Glutamat
GLUT1 : *Glucose Transporter 1*
GLY : *Glycine*
HDAC : *Histone Deacetylases*
HER2 : *Human Epidermal Growth Factor 2*
HIV : *Human Immunodeficiency Virus*
HPV : *Human Papilloma Virus*
HR-HPV : *High Risk Human Papilloma Virus*

HSIL : *High-Grade Squamous Intraepithelial Lesion*

IFN : Interferon

IVA : Inspeksi Visual Asam Asetat

KDR : *Kinase Domain Receptor*

KGB : Kelenjar Getah Bening

KIS : Karsinoma In Situ

LBDD : *Ligan Based Drug Design*

LEEP : *Loop Excision Electrocauterprocedure*

LEU : *Leucine*

LGA : *Lamarckian Genetic Algorithm*

LLETZ : *Large Loop Excision Of The Transformation Zone*

LR-HPV : *Low Risk Human Papilloma Virus*

LSIL : *Low-Gradesquamous Intraepithelial Lesion*

LVSI : *Lymph-Vascular Space Invasion*

MAPK : *Mitogen Activated Protein Kinase*

MEK : *Methyl Ethyl Ketone*

NF-kB : *Nuclear Factor Kappa B*

NIS : Neoplasia Intraepitel Serviks

NK : *Natural Killer*

NOS : *Not Otherwise Specified*

PARP : *Poly (ADP-Ribose) Polymerase*

PDB : Protein Data Bank

PHE : *Phenylalanine*

pRB : Protein Retinoblastoma

QSAR : *Quantitative Structure Activity Relationship*

RMSD : *Root Mean Square Deviation*

ROS : *Reactive Oxygen Species*

SBDD : *Structure Base Drug Design*

SIL : *Squamous Intraephitelial Lesion*

SMILES : *Simplified Molecular Input Line Entry System*

TGF : *Transforming Growth Fctor*

TNF : *Tumor Necrosis Factor*

mTOR : *Mammalian Target Of Rapamycin*

TRAIL : *TNF-Related Apoptosis Inducing Ligand*

VEGF : *Vascular Endothelial Growth Factor*

VEGFR : *Vascular Endothelial Growth Factor Receptor*

BAB 1
PENDAHULUAN

1.1 Latar Belakang

Kanker serviks adalah salah satu penyebab utama kematian akibat kanker pada perempuan di seluruh dunia dan secara epidemiologi mirip dengan penyakit kelamin dengan tingkat penularan rendah.[1] Pada tahun 2022, diperkirakan terdapat 660.000 kasus baru dari kanker serviks dengan angka kematian sebanyak 350.000 di seluruh dunia.[2] Hal ini menjadikan kanker serviks memimpin di posisi ketiga sebagai kanker paling banyak di dunia setelah kanker payudara dan kanker kolorektal.[3] Jenis HPV yang berperan dalam kanker serviks adalah HPV risiko tinggi diantaranya yang paling umum yaitu, HPV 16 dan 18 menyebabkan 70% kanker serviks di seluruh dunia.[4] Menurut data *Globocan* tahun 2022, kanker serviks menempati urutan kedua dengan kasus baru tertinggi dengan angka 36.964 kasus atau 16,8% dari total kasus kanker di Indonesia.[5] Menurut data Sumatera Selatan, terdapat 887 kasus kanker serviks pada tahun 2019 dan 953 kasus pada tahun 2020. Kasus kanker serviks di Palembang cenderung mengalami peningkatan setiap tahun, terdapat 468 kasus kanker serviks pada tahun 2021 dan 589 kasus pada tahun 2022.[6]

Data statistik yang dikumpulkan oleh American Cancer Society mengungkapkan bahwa tingkat kematian akibat kanker hanya mengalami sedikit perubahan selama 50 tahun terakhir.[7] Keberhasilan terapi kanker serviks berbeda-beda antar stadium penyakit, stadium 1 dengan presentase 85%, stadium II 60%, dan stadium III adalah 40%. Akan tetapi, diagnosis kanker serviks berbeda-beda antar stadium penyakit. Sebagian besar pasien didiagnosis pada stadium pertengahan hingga akhir (35% stadium II, 44% stadium III, dan 8% stadium IV) dan hanya sebagian kecil pasien yang menunjukkan gejala kanker serviks.[8]

Kasus baru kanker serviks sekitar 83% dan angka kematian sebesar 88% terjadi di negara-negara berkembang. Walaupun terdapat kemajuan penting dalam

pengetahuan mengenai kanker serviks sebagai penyakit yang dapat dicegah, masih belum ada perbaikan dalam kelangsungan hidup pasien sehingga beban penyakitnya masih tinggi.[9] Terapi kanker serviks meliputi radioterapi, kemoterapi, dan imunoterapi. Mekanisme kerja setiap terapi berbeda-beda untuk menghambat pembelahan sel dan proliferasi sel yang tumbuh dengan cepat.[10] Penambahan bevacizumab pada kemoterapi telah menjadi satu-satunya kemajuan signifikan baru-baru ini dalam pengobatan kanker serviks yang berulang dan metastatik.[11] Bevacizumab bekerja dengan cara mengikat VEGF yang beredar secara selektif, sehingga menghambat ikatan VEGF dengan reseptor permukaan selnya dan akan menghambat angiogenesis tumor.[12] Masalah umum dari terapi kanker ini adalah terjadinya resistensi terhadap banyak obat onkologis, termasuk anti-angiogenik.[13]

Vascular Endothelial Growth Factor (VEGF) diproduksi oleh banyak jenis sel termasuk sel tumor, makrofag, trombosit, keratinosit, dan sel mesangial ginjal. Strategi anti-VEGF untuk mengobati kanker dirancang untuk menargetkan fungsi pro-angiogenik VEGF lalu menghambat neovaskularisasi.[14] VEGF merupakan biomarker signifikan yang menyebabkan angiogenesis tumor. Hasil studi menunjukkan peningkatan ekspresi VEGF dihubungkan dengan prognosis yang tidak baik pada kanker serviks membuat ekspresi VEGF dapat diperiksa secara rutin untuk menentukan prognosis dari pasien kanker serviks. Hasil penelitian ini mengarahkan bahwa terapi anti-VEGF mempunyai peran penting dalam penyembuhan kanker serviks.[15]

Resistensi yang terjadi terhadap obat anti-angiogenik bevacizumab masih menjadi masalah dalam terapi kanker dan penemuan senyawa bioaktif terbaru akan sangat membantu sebagai terapi alternatif kanker serviks.[13] Emodin merupakan turunan antrakuinon alami yang dapat ditemukan pada akar dan daun berbagai tanaman, jamur, dan lumut.[16] Emodin dikenal terutama sebagai tirosin kinase inhibitor dan menunjukkan aktivitas farmakologis yang serbaguna seperti antineoplastik, antiinflamasi, antiangiogenesis, antidiabetik, dan fungsi antimikroba, baik *in vitro* maupun *in vivo*, dan menunjukkan sitotoksisitas terhadap berbagai sel kanker.[17] Emodin terutama diisolasi dari *Rheum palmatum* atau disebut juga rhubarb Cina yang dapat dimakan. Emodin juga ditemukan dalam banyak

spesies jamur termasuk genus *Aspergillus*, *Pyrenochaeta*, dan *Pestalotiopsis*.[18] Beberapa hasil penelitian menunjukkan emodin menghambat proliferasi, migrasi, dan pembentukan sel endotel yang distimulasi dengan VEGF. Hal ini menandakan emodin merupakan senyawa bioaktif yang bekerja sebagai anti-VEGF dan mungkin dapat berguna untuk terapi kanker serviks.[19]

Metode komputasional telah menjadi perkembangan teknologi yang dapat mempermudah *drug discovery process* saat ini. *Drug discovery process* merupakan proses mengidentifikasi dan mengkarakterisasi molekul dengan potensi secara aman memodulasi penyakit dengan tujuan memberikan obat yang dapat meningkatkan kualitas hidup pasien. *Drug discovery* adalah proses yang panjang dan membutuhkan sumber daya yang intensif dan memerlukan kerja sama erat terhadap berbagai disiplin ilmu.[20] Pendekatan komputasi akan menjadi alat yang berguna untuk menafsirkan dan memandu eksperimen dengan metode *in silico* agar mempercepat proses desain obat, pendekatan ini biasa disebut dengan *Computer-aided Drug Design* (CADD).[21] Salah satu metode dari CADD adalah *molecular docking*. *Molecular docking* telah menjadi aspek penting dalam pengembangan obat *in silico.* Teknik ini melibatkan prediksi interaksi antara molekul dan protein pada tingkat atomik. Hal ini memungkinkan peneliti untuk mempelajari perilaku molekul dalam situs pengikatan protein target dan memahami proses biokimia yang mendasari interaksi tertentu.[22]

Penelitian mengenai alternatif pengobatan kanker serviks menggunakan senyawa bioaktif yang memiliki target spesifik akan sangat membantu bidang biomedis. *Molecular docking* dapat memprediksi interaksi antara senyawa bioaktif emodin terhadap reseptor VEGF pada kanker serviks untuk dilakukan pengujian lanjutan. Alasan tersebut serta belum banyaknya penelitan mengenai interaksi emodin terhadap reseptor VEGF pada kanker serviks menjadi latar belakang dilakukannya penelitian ini.

1.2 Rumusan Masalah

Bagaimana interaksi senyawa bioaktif emodin terhadap reseptor VEGF pada kanker serviks?

1.3 Tujuan Penelitian

1.3.1 Tujuan Umum

Penelitian ini memiliki tujuan untuk mengtahui bagaimana interaksi dari senyawa bioaktif emodin terhadap reseptor VEGF pada kanker serviks.

1.3.2 Tujuan Khusus

Adapun tujuan khusus dari penelitian ini adalah sebagai berikut :

1. Untuk menganalisis ikatan yang terbentuk antara emodin dan reseptor VEGF.
2. Menemukan pose terbaik dari ikatan yang terbentuk antara emodin dan reseptor VEGF.
3. Mendapatkan skor docking dari interaksi emodin dan reseptor VEGF.

1.4 Hipotesis Penelitian

Terdapat interaksi antara senyawa emodin terhadap reseptor VEGF pada kanker serviks.

1.5 Manfaat Penelitian

1.5.1 Manfaat Teoritis

Penelitian ini diharapkan dapat digunakan menjadi studi dasar untuk penelitian lebih lanjut mengenai topik terkait dengan manfaat senyawa bioaktif emodin sebagai terapi alternatif kanker serviks.

1.5.2 Manfaat Tata Laksana

Hasil penelitian diharapkan dapat menjadi salah satu bahan pertimbangan dalam pelaksanaan penelitian lebih lanjut mengenai penggunaan senyawa bioaktif emodin sebagai agen terapi kanker serviks.

1.5.3 Manfaat Subjek

Hasil penelitian diharapkan dapat berguna menjadi salah satu sumber pengetahuan terkait hubungan antara konsumsi senyawa bioaktif emodin dengan kejadian kanker serviks.

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