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# Docking Molecular Study, Pharmacokinetics Profile and Toxicity Prediction of Basil Plant (*Ocimum basillicum*) Compounds as Isositrate Dehydrogenase Inhibitior

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***ABSTRACT***

*This study aims to predict the compounds from Ocimum basillicum that have potential as enzyme isocitrate dehydrogenase (IDH) inhibitors. Forty-two compounds from Ocimum basillicum were carried out by molecular docking to the IDH enzyme using the AutodockTools 1.5.7 program and continued prediction of pharmacokinetic profile and toxicity using ADMETab 2.0 and Toxtree. The validation of the molecular docking method showed an RMSD value of 1.3752 A. As a result of the research, we discovered several compounds had the best interactions in our investigation. Those compounds were Apigenin, Catechin, Chloronergic Acid, Ellagic Acid, Quercetin, Rosmarinic Acid, Rutin, Eriodictyol, and Chicoric Acid, with binding affinity values of -7.5, -7.2, -7.6, -7.9, -8.0, -7.6, -7.9, and -7.1, respectively. Several compounds are predicted to have the potential to be developed as IDH inhibitors. Furthermore, the ADMET's predictions show that these potential compounds still require improvement in pharmacokinetics and toxicity. However, further laboratory investigations like in vitro and in vivo assays need to be conducted.*

***KEYWORDS****: Molecular Dcking, Ocimum basillicum, Isositrate Dehidrogenase, Cancer.*

## INTRODUCTION

The enzyme isocitrate dehydrogenase (IDH) is an important enzyme that participates in several metabolic processes, such as the Krebs cycle, glutamine metabolism, regulation of lipogenesis, and redox. IDH1 is in the cytoplasm and peroxisomes (S. Han et al., 2020). In humans, IDH enzymes catalyze the conversion of isocitrate to α-ketoglutarate (α-KG), an intermediate in the citric acid cycle. Specific mutations in the genes encoding IDHs cause neomorphic enzymatic activity that produces D-2-hydroxyglutarate (2-HG) and inhibits α-KG-dependent enzymes such as histone and DNA demethylases. Therefore, IDH mutations result in hypermethylated DNA

and histone profile, which is considered to be among the major mechanisms behind tumorigenesis (Kayabolen et al., 2021)

Mutations in IDH are prevalent in human malignancies. IDH mutations also occur in acute myeloid leukemia (AML), myelodysplastic syndrome (MSD), myeloproliferative neoplasms (MPN), cholangiocarcinoma, enchondroma and chondrosarcoma, and other types of cancer. In the integrated genomic analysis of human glioblastoma (GBM), IDH mutations were observed in 12% of GBM samples. They were predominantly in tumors developed from low-grade gliomas (secondary GBM). Furthermore, >70% of WHO grade II/III gliomas were found to have IDH mutations (C. H. Han & Batchelor, 2017) It has become clear that IDH mutations are associated with many epigenetic and metabolic changes in these tumors.

Surgery, radiotherapy, and chemotherapy are used in various clinical treatments for tumors and cancer patients (Yi et al., 2013). Chemotherapy is routinely used in cancer treatment because it can kill more cancer cells in a shorter period of time. However, this also causes a variety of toxicities that can affect therapy results. Long-term use can cause normal cells to lose functionality and make cancer cells susceptible to this treatment (Desai et al., 2008). Alternative medical therapy is the best solution by searching for new molecules that come from nature and can act against cancer cells without having side effects that can cause toxicity (Wisbeck et al., 2020) *Ocimum basillicum* is an essential oil that has been used in traditional medicine to treat various diseases and provides a good source of bioactive compounds for cancer prevention and treatment (Perna et al., 2022)

By designing and modifying drugs based on ligands (ligand-based drug design), which will predict the bonds affinity of various active compounds to establish biological activity relationships, molecular docking is in the form of a computational simulation that enables drug development to be carried out efficiently and effectively (Ziemska et al., 2020) and also the fastest way to identify drug candidates and their targets (Deshpande et al., 2020) Therefore, molecular docking plays an important role in terms of rational drug design (Nursamsiar et al., 2016)

Despite this, no research has investigated *Ocimum basillicum* compounds that are chemically and pharmacologically active as IDH inhibitors. Therefore, this study was carried out to predict the bioactive compounds from *Ocimum basillicum* that have the potential to be IDH inhibitors by molecular docking and prediction of pharmacokinetic profile and toxicity.

## MATERIAL AND METHODS

### Material and Instrument

The instrument used is a set of portable computers. The software used is the program package Notepad++, Autodock Tools 1.7.5, and the Biovia Discovery Studio Visualizer 2021 program used in the molecular docking process. Prediction of Pharmacokinetics profile and toxicity using ADMETab 2.0 (https://admetmesh.scbdd.com/)

### Methods

*Ligand Preparation*

The test compounds used for molecular docking were obtained according to (Avetisyan et al., 2017), (Fitsiou et al., 2016), (Dris et al., 2017), (Antonescu et al., 2021), (Aminian et al., 2022), (Hikmawanti et al., 2019), (Rezzoug et al., 2019), (Zarlaha et al., 2014), and (Kayabolen et al., 2021). Vorasidenib as the positive control and 42 bioactive compounds from *Ocimum basillicum* that have anticancer activity were selected for use in this study. The 3D conformations of all the ligan compounds were downloaded from PubChem(https://pubchem.ncbi.nlm.nih.gov ). The optimized three-dimensional structure using the Autodock Tools program by setting the rotatable bond. As for the native ligand used, AKG is a natural ligand from the 4L03 protein.

*Enzyme Preparation*

The IDH enzyme was downloaded from the RSCB.PDB website (https://www.rcsb.org) with PDB ID 4L03 in *.Sdv/* 3D format with its natural ligand is AKG *(2-Oxoglutaric Acid)*. The protein separated from all other components in the protein complex (protein molecules, other small molecules, ions, and water). The enzyme loaded with a Kollman Charge and will automaticly be saved.

*Docking Molecular*

The molecular docking was carried out using AutoDock Vina software assisted by AutoDockTools. The enzyme's active site was determined following the AKG ligand binding site with the enzyme. Molecular docking parameters were used according to the default value. The coordinate of the grid box and adjustment by X = -29,823, Y = -37,579, Z = 16,44 with a spacing of 0.375A. The molecular docking method is valid if the RMSD value obtained from the re-docking of the native ligand is less than 2 Å (Prasetiawati et al., 2021). Furthermore, the visualization results can be seen using the Biovia Discovery Studio Visualizer by docking between the enzyme and ligand. Visualization can be analyzed based on the interaction of amino acids with the enzymes

*Profil Pharmacokinetics and Toxicity Prediction*

This prediction was performed using the ADMETlab 2.0 network-lined instrument (https://admetmesh.scbdd.com) from Computational Biology. Testing is done by uploading the ligands of the *Ocimum basillicum* compounds in *smile format

## RESULTS AND DISCUSSION

### Validation of Doking Method

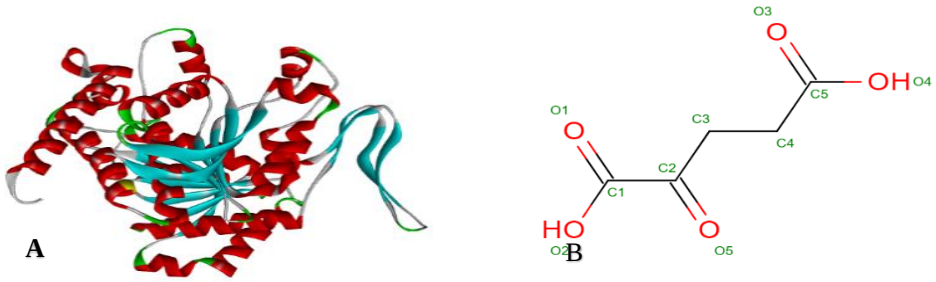


Figure 1. IDH Receptor (A), AKG Natural Ligand (B)

Figure one, IDH enzyme is the crystallography structure of cytosolic enzyme Isocitrate Dehydrogenase (IDH1) complexed with NADP+ and Ca2+alpha. The first step in molecular docking is a validation of the docking method. This validation method begins with ligand and enzyme preparation by removing the other components in the enzyme complex (enzyme molecules, other small molecules, ions, and water). The addition of Kollman charges to the target provide a charge on the amino acid residue in the form of electrostatic potential energy based on quantum mechanical calculations(Kolina et al., 2019). An RMSD value 1.3752 A was obtained after 10 times redocking the 4L03 protein with the AKG ligand. These results showed that the docking method is valid. A separation was carried out between the target protein and the natural ligand to validate the docking method, as seen in Figure 1.

### Bonding Energy (ΔG)

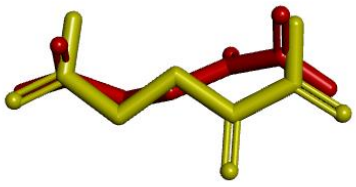

Figure 2. Ligand AKG(Yellow) and Redocking Ligand AKG(Red)

In order to get the docking results, the bond free energy (ΔG) score of the tested compound, enzyme complexes and the RMSD value were obtained. Bond-free energy indicates affinity between the ligand and the enzyme (Pantsar & Poso, 2018). Low affinity indicates that the ligand and the enzyme require low binding energy. Thus,

the lower ΔG score, the stronger and more stable the bond between the ligand and the enzyme (Syahputra et al., 2014). In addition, the analysis was also observing the interactions that occur between ligands and amino acid residues in enzyme. The ΔG score of the test compound's native ligand and positive control can be seen in Table 1.

The AKG show ΔG score -5,3 while positive control Vorasidenib -6,8. Meanwhile, out of the 42 test compounds have a different binding affinity of each ligand, several compounds had the lowest affinity values compared to the native ligand and the positive control : Apigenin, Catechin, Chologenic acid, Ellagic acid, Quercetin, Rosmarinic acid, Rutin, Eriodictyol, and chicoric acid with ΔG score is -7.5, -7.2, -7.6, -7.9, -8.0, -7.1, -7.9, -7.6, and -7.1 respectively. Veridiflorol and Ferulic acid has the same energy as the native ligand.

The result shows that the test compound with the lowest ΔG are Quarcetin, Rutin, and Ellagic acid in table 1.

| NO | COMPOUNDS | ΔG | NO | COMPOUNDS | ΔG |
|---|---|---|---|---|---|
| ***1*** | **Vorasidenib ($C^{14}H^{13}ClF^6N^6$)** | **-6,8** | 23 | Eugenol ($C^{10}H^{12}O^2$) | -4,7 |
| ***2*** | **AKG (Native Ligand)** | **-5,3** | 24 | Geranyl Acetate ($C^{12}H^{20}O^2$) | -4,8 |
| ***3*** | **Mycrene ($C^{10}H^{16}$)** | **-3,6** | 25 | Cinnamic Acid ($C^9H^8O^2$) | -4,8 |
| ***4*** | Camphene ($C^{10}H^{16}$) | -3,8 | 26 | Caryophyllene ($C^{15}H^{24}$) | -4,8 |
| ***5*** | Sabinene ($C^{10}H^{16}$) | -3,8 | 27 | Methyl Cinnamate ($C^{10}H^{10}O^2$) | -4,9 |
| ***6*** | Linalool ($C^{10}H^{18}O$) | -3,9 | 28 | Germacrane D ($C^{15}H^{30}$) | -5,1 |
| ***7*** | Citronellol ($C^{10}H^{20}O$) | -4,0 | 29 | Aromadendrene ($C^{15}H^{24}$) | -5,2 |
| ***8*** | Methyl Heptenone ($C^8H^{14}O$) | -4,0 | 30 | Cadinol ($C^{15}H^{26}O$) | -5,2 |
| ***9*** | Palmitic Acid ($C^{16}H^{32}O^2$) | -4,1 | 31 | Viridiflorol ($C^{15}H^{26}O$) | -5,3 |
| ***10*** | Citral ($C^{10}H^{16}O$) | -4,1 | 32 | Ferulic Acid ($C^{10}H^{10}O^4$) | -5,3 |
| ***11*** | Chavicol ($C^9H^{10}O$) | -4,2 | 33 | Terpenyl Acetate ($C^{12}H^{20}O^3$) | -5,5 |
| ***12*** | Geraniol ($C^{10}H^{18}O$) | -4,2 | 34 | Caffeic Acid ($C^9H^8O^4$) | -5,7 |
| ***13*** | Methyl Cavicol ($C^{10}H^{12}O$) | -4,2 | 35 | Gallic Acid ($C^7H^6O^5$) | -6,0 |
| ***14*** | Cyclopentylacetone ($C^8H^{14}O$) | -4,2 | 36 | **Rosmarinic Acid ($C^{18}H^{16}O^8$)** | **-7,1** |
| ***15*** | Camphor ($C^{10}H^{16}O$) | -4,4 | 37 | **Chicoric Acid ($C^{22}H^{18}O^{12}$)** | **-7,1** |
| ***16*** | Menthol ($C^{10}H^{20}O$) | -4,4 | 38 | **Catechin ($C^{15}H^{14}O^6$)** | **-7,2** |
| ***17*** | Eucalyptol | -4,4 | 39 | **Apigenin** | **-7,5** |

| | | | | | |
|---|---|---|---|---|---|
| | ($C^{10}H^{18}O$) | | | **($C^{15}H^{10}O^{5}$)** | |
| ***18*** | Phytol ($C^{20}H^{40}O$) | -4,4 | 40 | **Chloronergic Acid ($C^{16}H^{18}O^{9}$)** | **-7,6** |
| ***19*** | Nerylacetate ($C^{12}H^{20}O^{2}$) | -4,4 | 41 | **Eriodictyol ($C^{15}H^{12}O^{6}$)** | **-7,6** |
| ***20*** | Linalyl Acetate ($C^{12}H^{20}O^{2}$) | -4,5 | 42 | **Ellagic Acid ($C^{14}H^{6}O^{8}$)** | **-7,9** |
| ***21*** | Methyl Eugenol ($C^{11}H^{14}O^{2}$) | -4,5 | 43 | **Rutin ($C^{27}H^{30}O^{16}$)** | **-7,9** |
| ***22*** | Bergamotene ($C^{15}H^{24}$) | -4,7 | 44 | **Quarcetin ($C^{15}H^{10}O^{7}$)** | **-8,0** |

Table 1. ΔG Score of *Ocimum Basillicum* Compounds

Various studies state that these three compounds have potential in inhibiting cancer, quarcetin can improve cancer progression through various mechanisms: including down regulation of mutant p53 proteins, G1 phase arrest, tyrosine kinase inhibition, and down regulation of cell survival, proliferative and anti-apoptotic proteins(Lotfi et al., 2023), quercetin also significantly inhibited the proliferation of human Glioblastoma U251 cells(Y. Liu et al., 2017). Rutin has been shown to utilize numerous mechanisms to obstruct cancer initiation and progression by modulating several deregulated signaling pathways involved in apoptosis, inflammation, angiogenesis, and autophagy. Rutin has shown tremendous anticancer potential against a range of cancer cell lines including glioblastoma (Pandey et al., 2021). Rutin also inhibits lipid accumulation via reducing lipogenesis(Wu et al., 2011). While Ellagic acid inhibited proliferation and induced accumulation of the S-phase cells in the cell cycle, activated apoptosis pathway associated with caspase-3 activation, and enhanced ATRA-induced differentiation in human leukimia cell(Mertens-Talcott et al., 2003). Where the IDH mutation greatly affects the growth of glioblastoma(S. Han et al., 2020), lipogenesis(Filipp et al., 2012), and human leukemia cancer(Mckenney et al., 2013)

**Bond Interaction**

The docking results showed two types of hydrogen bonds: conventional hydrogen bonds (H-X) and carbon-hydrogen bonds (CH-X), Van Der Waals bonds, and salt bridge bonds between the binding sites of the 4L03 protein. In the interaction of the AKG-4L03 complex, there is one conventional hydrogen bonds interaction with the amino acids ASN:96, three Salt Bridge interactions in ARG:100, ARG:109 and ARG:132 and there are five Van Der Waals bonds see Figure 3A

The results of the bond interaction with the ten test compounds with the lowest ΔG score (see in table 2). Voradenib interacts to form 3 hydrogen bonds, 6 halogen bonds, 2 carbon hydrogen bonds, and 8 van der Waals bonds. Where the bond interactions are the same as AKG ligands in almost all amino acids except TYR:139 with a better predicted

activity mechanism. Where the halogen bond plays an important role in pharmacological activity which can increase parameters with improves the thermodynamic parameters of the system (ligand-receptor pair), and the dissociation constant (Kd) is positively modified, that plays important approach in lead optimization of drug development and increases the binding affinity and binding selectivity(Suárez-Castro et al., 2018)

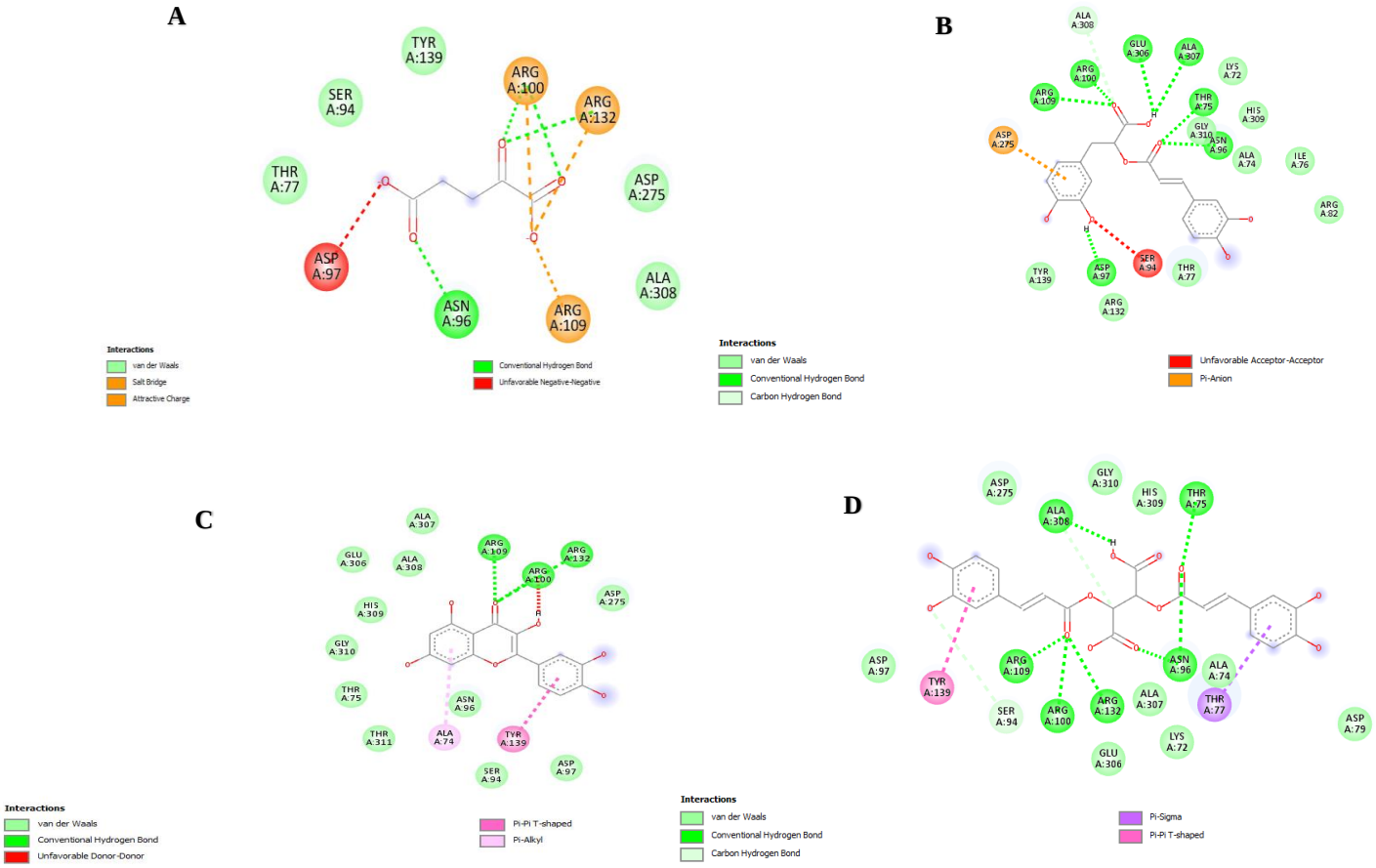


Figure 3. 2D Visualisation interaction of AKG-4L03 (A), Rosmarinic Acid-4L03(B), Quercetin-4L03(C), and Chicoric acid-4L03(D)

Based on table 2, the Quarcetin compound with the lowest ΔG score forms three hydrogen interactions with the same interactions with AKG as ARG:109, ARG:100, and ARG:132. In rutine compounds form four hydrogen bond interactions and three carbon hydrogen bonds, ARG:109, ARG:100, ASP:275 and THR:77 form the same interactions as native ligands. The same hydrogen bonding interaction on the amino acid ASN:96 is found in the compounds rosmarinic acid and chicoric acid, where Rosmarinic acid is the compound with the most hydrogen bond interactions, several of them have similar interactions with native ligand AKG in the amino acids ARG:109, ARG:100, ASN:96, and ALA:307. As for the Chicoric acid compound, the formation of interactions between the amino acids ASN:96, ARG:132,

ARG:100, ARG:109, and ALA:308 makes it the compound with the most interactions in common with AKG

Table 2. Bond Interaction of Ocimum Basillicum Compounds

| COMPOUNDS | AMINO ACID SEQUENCE | BOND INTERACTION | COMPOUNDS | AMINO ACID SEQUENCE | BOND INTERACTIONS |
|---|---|---|---|---|---|
| **Vorasidenib** | THR:311, THR:75, and ARG:109. | Hydrogen Interaction | AKG (Native Ligand) | ASN:96 | Hydrogen Interaction |
| | ASN:96, GLU:306, HIS:309, ALA:308, ALA:307 and THR:75. | Halogen Interaction | | ASP:100, ARG:132, and ARG:109 | Salt Bridge Interaction |
| | ILE:76 and GLY:310 | Carbon-Hydrogen Interaction | | THR:77, SER:94, TYR:139, ASP:275, and ALA:308 | Van der waals Interaction |
| | ARG:82, ALA:74, LYS:72, ARG:100, ARG:132, ASP:275, SER:94, THR:77 | Van der waals Interaction | | | |
| **Rosmarinic Acid** | ARG:109, ARG:100, GLU:306, ALA:307, THR:75, ASP:97 and ASN:96. | Hydrogen Interaction | Eriodictyol | THR:75, ARG:132, ARG:100, ARG:109, and ALA:307. | Hydrogen Interaction |
| | LYS:72, HIS:309, GLY:310, ALA:74, ILE:76, ARG:82, THR:77, ARG:132, TYR;139. | Van der waals Interaction | | SER:94, ASP:97, ASN:96, THR:311, GLY:310, ALA:74, HIS:309, ALA:308, GLU:306, ASP:275 | Van der waals Interaction |
| | ALA:308 | Carbon-Hydrogen Interaction | | | |
| **Chicoric Acid** | THR:75, ASN:96, ARG:132, ARG:100, ARG:109, ALA:308. | Hydrogen Interaction | Ellagic Acid | ARG:100, and ARG:132. | Hydrogen Interaction |
| | ASP:97, ASP:275, GLY:310, HIS:309, ALA:74, ASP:79, LYS:72, | Van der waals Interaction | | : LYS:72, ALA:307, ALA:74, ALA:308, GLU:306, GLY:310, THR:75, | Van der waals Interaction |

| | | | | | |
|---|---|---|---|---|---|
| | GLU:306, ALA:307. | | | THR:77, SER:94, TYR:139, ASP:275, And ASN:96 | |
| | SER:94 | Carbon-Hydrogen Interaction | | | |
| **Catechin** | ARG:100, and ALA 308. | Hydrogen Interaction | Rutin | ARG:109, ARG:100, ALA:307, and ASP:275. | Hydrogen Interaction |
| | TYR:272, ASP:275, ARG:109, ALA:307, HIS:309, GLY:310, THR:75, ASN:96, THR:311, SER:94, and ASP:97 | Van der waals Interaction | | TYR:139, ILE:76, VAL:276, ASP:279, HIS:309, ALA:74, ALA:308, LEU:288, THR:311, GLU:306, ASN:96, ARG:132, ASP:97. | Van der waals Interaction |
| | | | | SER:94, THR:77, GLY:310 | Carbon-Hydrogen Interaction |
| **Apigenin** | ARG:109, ARG:100, and ARG:132. | Hydrogen Interaction | Quarcetin | ARG:109, ARG:100, and ARG:132. | Hydrogen Interaction |
| | ASP:97, SER:94, ASP:275, ALA:307, GLU:306, ALA:308, HIS:309, LYS:72, ALA:74, THR:311, ASN:96. | Van der waals Interaction | | ALA:307, ALA:308, GLU:306, HIS:309, GLY:310, THR:75, THR:311, ASN:96, SER:94, ASP:97 and ASP:275 | Van der waals Interaction |
| | GLY:310 | Carbon-Hydrogen Interaction | | | |
| **Chlorogenic Acid** | ARG:109, ARG:100, HIS:309, and THR: | Hydrogen Interaction | Mycrene | ALA:307, THR:75, LYS:72, HIS:309, ALA:308, ARG:109, ASN:96, ARG:100, SER:94, ASP:97, ARG:132, and GLY:310 | Van der waals Interaction |
| | 77ARG:132, ASN:96, GLU:306, ALA:308, LYS:72, ALA:74, THR:75, GLY:310, TYR:272, TYR:139, ASP:275, SER:94, and GLN:138. | Van der waals Interaction | | | |
| | ALA:307 | Carbon-Hydrogen Interaction | | | |

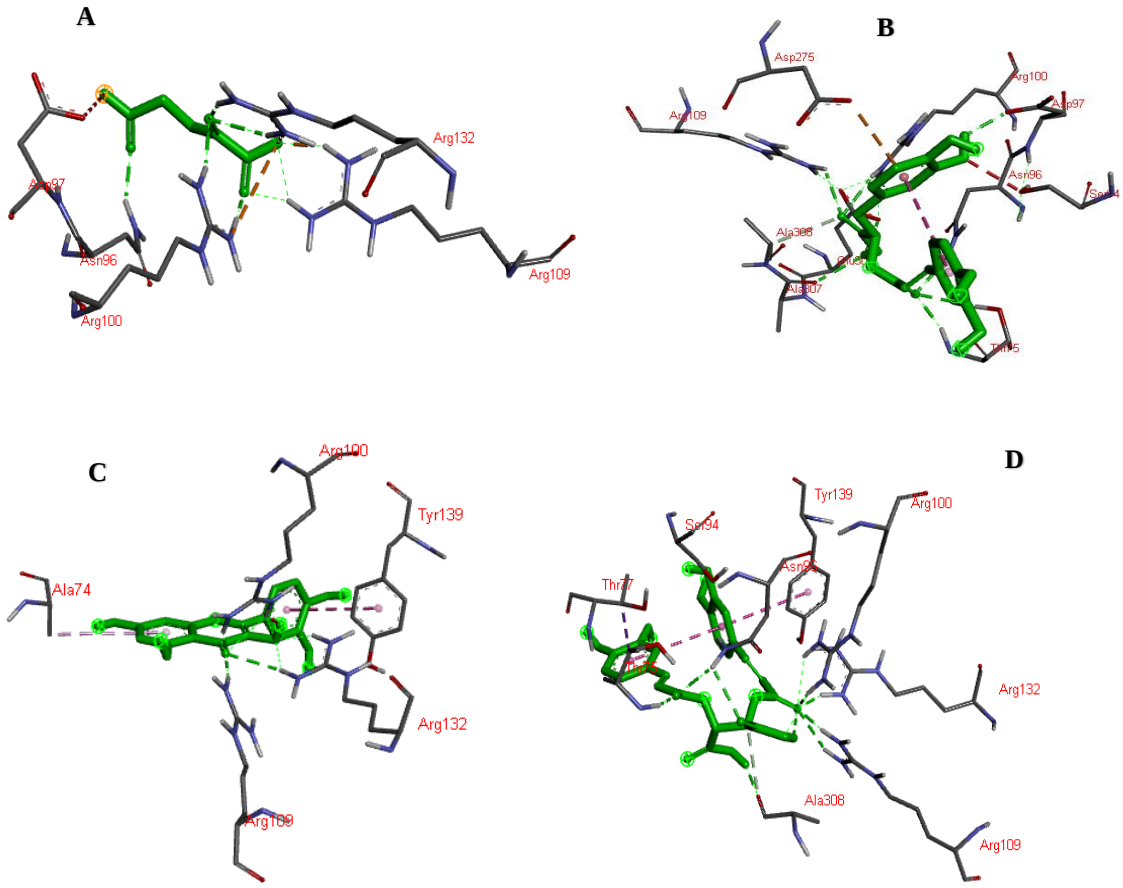


Figure 4. AKG-4L03 3D Interaction (A), Rosmarinic Acid-4L03 3D Interaction (B), Quercetin-4L03 3D Interaction (C), and Chicoric acid-4L03 3D Interaction (D)

The binding pose show that the O atom in every group compound is responsible for most of the hydrogen interactions that occur. The amino acids ARG:100 and ARG:109 in AKG interact with HH22 and HH12 atoms. In rosmarinic acid, oxypropanoic groups interact to form conventional hydrogen bonds with atoms HH22 and HH21 in the respective amino acids ARG:100 and ARG:109, the same thing also happens with Quarcetin in chromenone groups and as for Chicoric acid, the amino acids ARG:100 and ARG:109 interact in atom HH22 and HH12 with atom O in keton group (Figure 4), so it is predicted to have the possibility of having the same biological activity (Prasetiawati et al., 2021).Chicoric acid also have more interaction activity with amino acids than the native ligand. Where more conventional hydrogen bond interactions on bound amino acids are predicted to increase their activity (Frimayanti, Neni, Anita Lukman, 2021)

**Pharmacokinetics Profile and Toxicity**

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties play key roles in the development of drugs. This information is especially useful when to conduct environmental and human hazart assessment(Cheng et al., 2012). The most critical rate limiting step in the chemical safety assessment workflow is the availability of high quality data using the ADMETlab 2.0 instrument.

The ADME prediction was shown in table 3. In predicting absorption, vorasidenib cannot be absorbed properly in the intestinal, whereas chicoric acid cannot be absorbed in the intestine, while the Rosmarinic acid can be adsorbed well in all absorption parameters, goes along with it Rosmarinic Acid penetrated through Caco-2 cell monolayers and was detected by HPLC-PDA, thus, this study is evidence of the extensive of RA while penetrating through Caco-2 cells(Woottisin et al., 2022). In distribution prediction, all compounds have a poor bioavailability value. This is in accordance with the results of in vitro testing that rosmarinic acid have high hydrophilicity make it exhibit poor permeation across intestinal epithelial cells(Wang et al., 2017). As well as quarcetin has several health effects and theraphy, but the bioavailability unfortunately is poor(Kasikci & Bagdatlioglu, 2016). Only vorasidenib can't pass/penetrate across the blood-brain barrier. The research result show that a metaobnomic study demonstrated that Chicoric Acid has the ability to cross the blood-brain barrier(Q. Liu et al., 2017), due to the antioxidative effect of rosmarinic acid, it was thought that it may regulate this protein increase in astrocyte regulation. The weakening of microglial activation, Iba-1, an important biomarker for microglial activation, is thought to have its expression down-regulated, but the positive Iba-1 activity with the effect of rosmarinic acid is important to balance microglia activation. Where the immunohistochemical examination of IBA-1 and GFAP expressions is traumatic brain injury associated with the blood-brain barrier(Özevren et al., 2020). In metabolism prediction, Rosmarinic acid and Quarcetin can metabolism up to 15-20% of undergoing phase I metabolism, while chicoric acid predicted to have a poor metabolism. In excretion parameters, Rosmarinic acid has the highest score in clearance test, it becomes to predicted to have the best excretion

Table 3. ADME Prediction

| NO | COMPOUNDS | ABSORBTION | | | DISTRIBUTION | | | | METABOLISM | | | EKSKRETION | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Caco-2** | **HIA** | **MDCK** | **VDss** | **PPB** | **Fu** | **BBB** | **CYP 3A4** | **CYP 2D6** | **CYP P2C9** | **Total Clearance** | **T 1/2** |
| **1** | Vorasidenib | -4.166 | --- | 3.2e-05 | 4.144 | 96.862% | 3.240% | +++ | ++ | --- | - | 4.546 | 0.338 |
| **2** | Rosmarinic Acid | -6.005 | --- | 6.9e-06 | 0.369 | 97.722% | 2.043% | --- | --- | --- | + | 15.347 | 0.959 |
| **3** | Chicoric Acid | -6.450 | + | 9.2e-06 | 0.296 | 98.828% | 1.655% | --- | --- | --- | - | 4.971 | 0.974 |
| **4** | Quarcetin | -5.204 | --- | 7.7e-06 | 0.579 | 95.496% | 7.423% | --- | - | - | + | 8.284 | 0.929 |

The toxicity prediction (see table 4), Quarcetion has a toxic probability of being carcinogenic, but the in vivo and in vitro results show that quercetin classified as relatively safe and practically non-toxic for human use(Vitro et al., 2020). Vorasidenib is also predicted to have serious effects on human health because of its ability to damage genomes or interfere with cellular metabolic processes(Xiong et al., 2021)

Table 4. Toxicity Prediction

| NO | COMPOUNDS | TOXICITY | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | TOXICOPHORE | |
| | | **AMES Toxicity** | **Rat Oral Acute Toxicity** | **Carcinogencity** | **FDAMDD** | **Genotoxic Carcinogenicity Rule** | **NonGenotoxic Carcinogenicity Rule** |
| **1** | Vorasidenib | --- | --- | +++ | +++ | 1 alert(s) | 0 alert(s) |
| **2** | Rosmarinic Acid | --- | - | -- | --- | 1 alert(s) | 1 alert(s) |
| **3** | Rosmarinic Acid | --- | - | -- | --- | 1 alert(s) | 1 alert(s) |
| **4** | Quarcetin | + | --- | --- | - | 0 alert(s) | 0 alert(s) |

## CONCLUSION

This study indicated that the compound Quarcetin has the smallest binding free energy of -8.5, while the most hydrogen bond in ligan interaction is Rosmarinic acid with seven hydrogen bonds in amino acids including ARG:109, ARG:100, GLU:306, ALA:307, THR:75, ASP:97 and ASN:96. Meanwhile, Chicoric acid becomes a compound with the same of amino acid interactions with the native AKG ligand, so it is predicted to have the same biological activity, these compounds with the highest affinities are predicted to be developed as potential IDH inhibitors, While the results of the pharmacokinetic and toxicity profiles showed that rosmarinic acid and quarcetin are well absorbed, while chicoric acid cannot be absorbed in intestinene. The four

compound have good bioavailability value, and not meant to be toxic compound so they are safe to use. However, further laboratory investigations must be conducted, like in vitro and in vivo assays.

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