

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

*by* Yusnita Rifai

---

**Submission date:** 23-Jun-2023 09:35AM (UTC+0700)

**Submission ID:** 2121179360

**File name:** 37548-Article\_Text-115767-1-10-20230612.pdf (689.87K)

**Word count:** 5520

**Character count:** 29511



## Docking Molecular Study, Pharmacokinetics Profile and Toxicity Prediction of Basil Plant (*Ocimum basilicum*) Compounds as Isocitrate Dehydrogenase Inhibitor

Fitril Imani<sup>1</sup>, Yusnita Rifai<sup>1</sup>, Herlina Rante<sup>1</sup>, Ansari Masri<sup>2</sup>, Andri Anugerah Pratama<sup>3</sup>, Musabbiha<sup>3</sup>

22

<sup>1</sup>Departement of Pharmacy, Faculty of Pharmacy, Hasanuddin University, Makassar<sup>2</sup>Departement of Pharmacy, Faculty of Medicine and Health Science, Muhammadiyah University of Makassar<sup>3</sup>Departement of Pharmacy, Faculty of Medicine and Health Science, Alauddin Islamic State University of Makassar

\*Corresponding author e-mail: fitrilimani@gmail.com

### ABSTRACT

33

This study aims to predict the compounds from *Ocimum basilicum* that have potential as enzyme isocitrate dehydrogenase (IDH) inhibitors. Forty-two compounds from *Ocimum basilicum* 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 Å. As a result of the research, we discovered several compounds had the best interactions in our investigation. Those compounds were Apigenin, Catechin, Chlorogenic 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 basilicum*, Isocitrate Dehydrogenase, 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  $\alpha$ -ketoglutarate ( $\alpha$ -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  $\alpha$ -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 ligand 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 automatically 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 0.375Å. 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

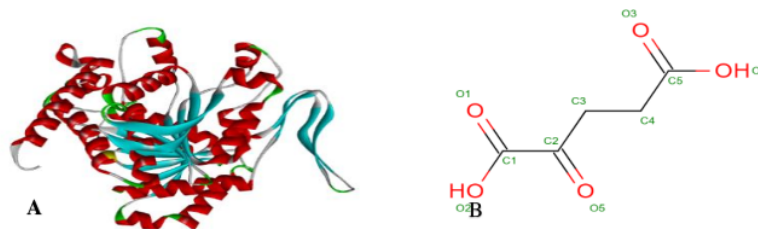


Figure 1. IDH Receptor (A), AKG Natural Ligand (B)

Figure one, IDH enzyme is the crystallography structure of cytosolic enzyme Isocitrate Dehydrogenase (IDH1) complexed with NADP+ and Ca<sup>2+</sup>-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 <sup>13</sup> 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 Å 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 ( $\Delta G$ )

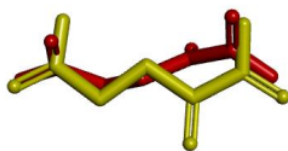


Figure 2. Ligand AKG (Yellow) and Redocking Ligand AKG (Red)

In order to get the docking results, the bond free energy ( $\Delta G$ ) 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  $\Delta G$  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  $\Delta G$  score of the test compound's native ligand and positive control can be seen in Table 1.

The AKG show  $\Delta G$  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  $\Delta G$  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  $\Delta G$  are Quercetin, Rutin, and Ellagic acid in table 1.

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

	(C <sup>10</sup> H <sup>18</sup> O)			(C <sup>15</sup> H <sup>10</sup> O <sup>5</sup> )	
18	Phytol (C <sup>20</sup> H <sup>40</sup> O)	-4,4	40	<b>Chlorogenic Acid</b> (C <sup>16</sup> H <sup>18</sup> O <sup>9</sup> )	<b>-7,6</b>
19	Nerylacetate (C <sup>12</sup> H <sup>20</sup> O <sup>2</sup> )	-4,4	41	<b>Eriodictyol</b> (C <sup>15</sup> H <sup>12</sup> O <sup>6</sup> )	<b>-7,6</b>
20	Linalyl Acetate (C <sup>12</sup> H <sup>20</sup> O <sup>2</sup> )	-4,5	42	<b>Ellagic Acid</b> (C <sup>14</sup> H <sup>6</sup> O <sup>8</sup> )	<b>-7,9</b>
21	Methyl Eugenol (C <sup>11</sup> H <sup>14</sup> O <sup>2</sup> )	-4,5	43	<b>Rutin</b> (C <sup>27</sup> H <sup>30</sup> O <sup>16</sup> )	<b>-7,9</b>
22	Bergamotene (C <sup>15</sup> H <sup>24</sup> )	-4,7	44	<b>Quercetin</b> (C <sup>15</sup> H <sup>10</sup> O <sup>7</sup> )	<b>-8,0</b>

Table 1. ΔG Score of *Ocimum Basillicum* Compounds

Various studies state that these three compounds have potential in inhibiting cancer, quercetin 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 leukemia 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

dissociation constant ( $K_d$ ) is positively modified, that plays important approach in

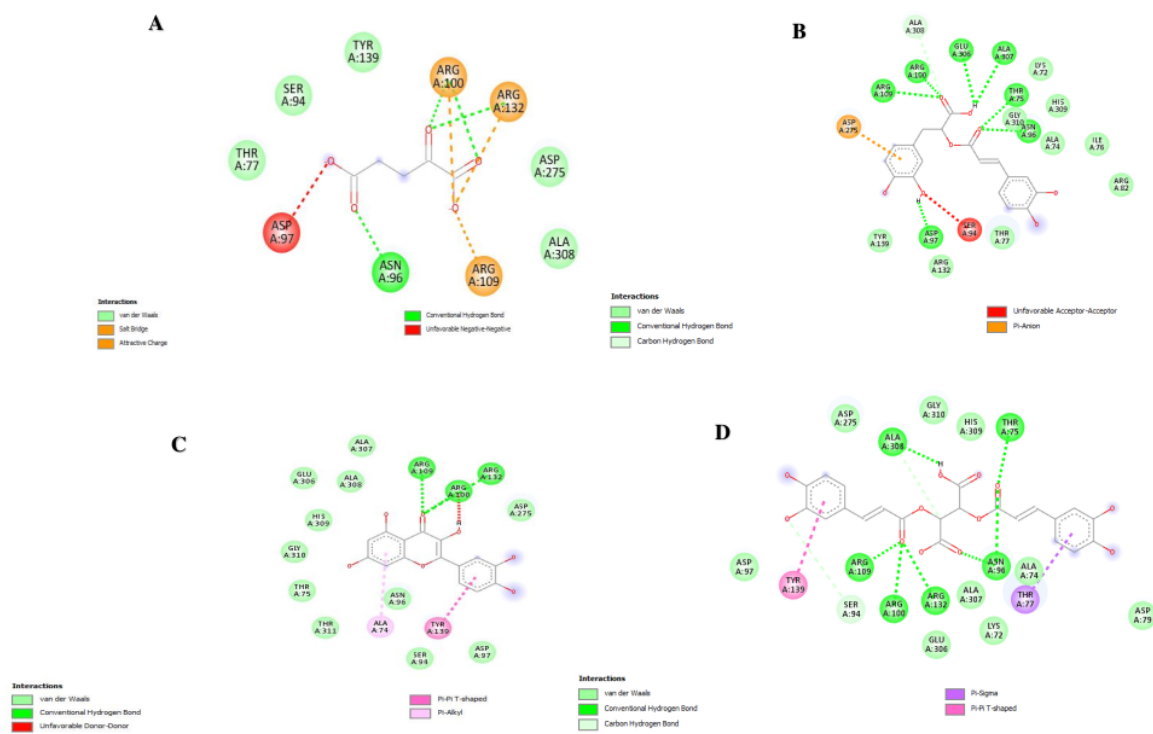


Figure 3. 2D Visualisation interaction of AKG-4L03 (A), Rosmarinic Acid-4L03(B), Quercetin-4L03(C), and Chicoric acid-4L03(D)

activity which can increase parameters with improves the thermodynamic parameters of the system (ligand-receptor pair), and

Based on table 2, the Quercetin compound with the lowest  $\Delta G$  score forms three hydrogen interactions with the same interactions with AKG as ARG:109, ARG:100, and ARG:132. In routine 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

lead optimization of drug development and increases the binding affinity and binding selectivity(Suárez-Castro et al., 2018)

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
<b>Vorasicidenib</b>	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			
<b>Rosmarinic Acid</b>	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			
<b>Chicoric Acid</b>	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, SER:94	Carbon-Hydrogen Interaction		THR:77, SER:94, TYR:139, ASP:275, And ASN:96	
<b>Catechin</b>	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
<b>Apigenin</b>	ARG:109, ARG:100, and ARG:132.	Hydrogen Interaction	Quarceetin	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. GLY:310	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
		Carbon-Hydrogen Interaction			
<b>Chlorogenic Acid</b>	ARG:109, ARG:100, HIS:309, and THR: 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. ALA:307	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
		Van der waals Interaction			
		Carbon-Hydrogen Interaction			

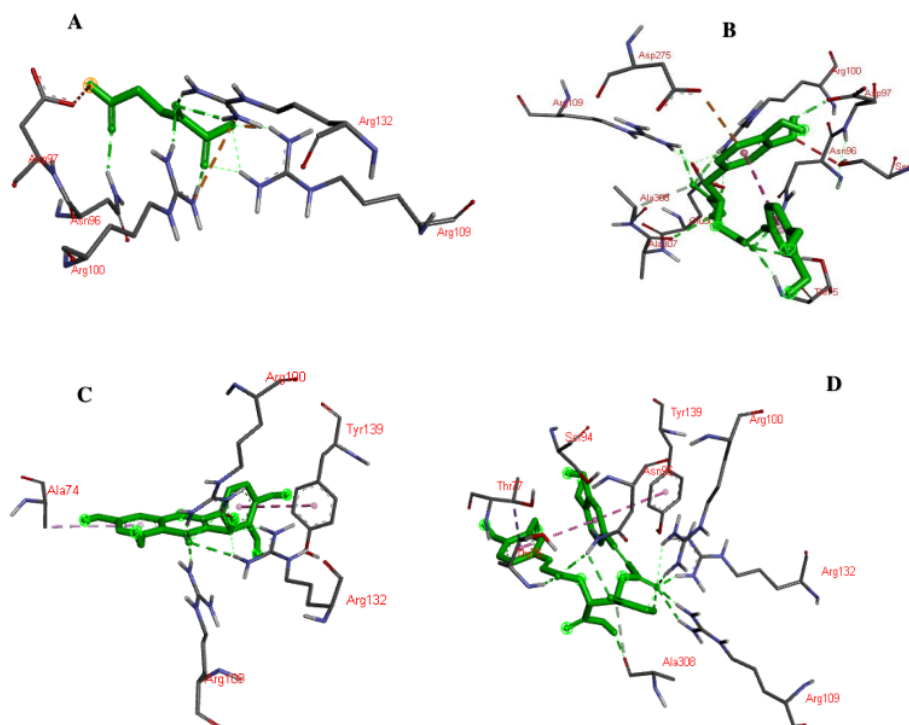


Figure 4. AKG-4L03 3D Interaction (A), Rosmarinic Acid-4L03 3D Interaction (B), Quercetin-4L03 3D Interaction (C), and Chicoric acid-4L03 3D Interaction (D)

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 Quercetin 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 hazard 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 therapy, 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	COMPOUN DS	ABSORPTION			DISTRIBUTION				METABOLISM			EKSRETION	
		Cac o-2	HI A	MD CK	VDss	PPB	Fu	BB B	CY P 3A4	CY P 2D6	CY P2C 9	Total Clearance	T 1/2
1	Vorasicenib	- 4.16 6	---	3.2e -05	4.144	96.86 2%	3.24 0%	+++	++	---	-	4.546	0.33 8
2	Rosmarinic Acid	- 6.00 5	---	6.9e -06	0.369	97.72 2%	2.04 3%	---	---	---	+	15.347	0.95 9
3	Chicoric Acid	- 6.45 0	+	9.2e -06	0.296	98.82 8%	1.65 5%	---	---	---	-	4.971	0.97 4
4	Quarctetin	- 5.20 4	---	7.7e -06	0.579	95.49 6%	7.42 3%	---	-	-	+	8.284	0.92 9

The toxicity prediction (see table 4), Quarctetin 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). Vorasicenib 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	Carcino gencity	FDAM DD	Genotoxic Carcinogenicit Rule	NonGenotoxic Carcinogenicity Rule	
1	Vorasicenib	---	---	+++	+++	10 1 alert(s)	0 alert(s)	
2	Rosmarinic Acid	---	-	--	---	10 1 alert(s)	1 alert(s)	
3	Rosmarinic Acid	---	-	--	---	10 1 alert(s)	1 alert(s)	
4	Quarctetin	+	---	---	-	0 alert(s)	0 alert(s)	

## CONCLUSION

This study indicated that the compound Quarctetin has the smallest binding free energy of -8.5, while the most hydrogen bond in ligand 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 intestine. 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](#).

## REFERENCES

- Aminian, A. R., Mohebbati, R., & Boskabady, M. H. (2022). The Effect of *Ocimum basilicum* L. and Its Main Ingredients on Respiratory Disorders: An Experimental, Preclinical, and Clinical Review. *Frontiers in Pharmacology*, *12*(January), 1–14. <https://doi.org/10.3389/fphar.2021.805391>
- Antonescu, A. I., Miere, F., Fritea, L., Ganea, M., Zdrinca, M., Dobjanschi, L., Antonescu, A., Vicas, S. I., Bodog, F., Sindhu, R. K., & Cavalu, S. (2021). Perspectives on the combined effects of *ocimum basilicum* and *trifolium pratense* extracts in terms of phytochemical profile and pharmacological effects. *Plants*, *10*(7). <https://doi.org/10.3390/plants10071390>
- Avetisyan, A., Markosian, A., Petrosyan, M., Sahakyan, N., Babayan, A., Aloyan, S., & Trchounian, A. (2017). Chemical composition and some biological activities of the essential oils from basil *Ocimum* different cultivars. *BMC Complementary and Alternative Medicine*, *17*(1), 1–8. <https://doi.org/10.1186/s12906-017-1587-5>
- Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., Lee, P. W., & Tang, Y. (2012). AdmetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *Journal of Chemical Information and Modeling*, *52*(11), 3099–3105. <https://doi.org/10.1021/ci300367a>
- Desai, A., Qazi, G., Ganju, R., El-Tamer, M., Singh, J., Saxena, A., Bedi, Y., Taneja, S., & Bhat, H. (2008). Medicinal Plants and Cancer Chemoprevention. *Current Drug Metabolism*, *9*(7), 581–591. <https://doi.org/10.2174/138920008785821657>
- Deshpande, R. R., Pandey, A., Nyayanit, N., & Modak, M. (2020). *Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information. January.*
- Dris, D., Tine-Djebbar, F., Bouabida, H., & Soltani, N. (2017). Chemical composition and activity of an *Ocimum basilicum* essential oil on *Culex pipiens* larvae: Toxicological, biometrical and biochemical aspects. *South African Journal of Botany*, *113*, 362–369. <https://doi.org/10.1016/j.sajb.2017.09.013>
- Filipp, F. V., Scott, D. A., Ronai, Z. A., Osterman, A. L., & Smith, J. W. (2012). Reverse TCA cycle flux through isocitrate dehydrogenases 1 and 2 is required for lipogenesis in hypoxic melanoma cells. *Pigment Cell and Melanoma Research*, *25*(3), 375–383. <https://doi.org/10.1111/j.1755-148X.2012.00989.x>
- Fitsiou, E., Mitropoulou, G., Spyridopoulou, K., Tiptiri-Kourpeti, A., Vamvakias, M., Bardouki, H., Panayiotidis, M. I., Galanis, A., Kourkoutas, Y., Chlichlia, K., & Pappa, A. (2016). Phytochemical profile and evaluation of the biological activities of essential oils derived from the greek aromatic plant species *Ocimum basilicum*, *Mentha spicata*, *Pimpinella anisum* and *Fortunella margarita*. *Molecules*, *21*(8), 1–15. <https://doi.org/10.3390/molecules21081069>
- Frimayanti, Neni, Anita Lukman, L. N. (2021). DEN-2 NS2B / NS3 serine protease. *Chempublish Journal Vol. 6 No. 1 (2021) 54-62 Studi*, *6*(1), 54–62.
- Han, C. H., & Batchelor, T. T. (2017). Isocitrate dehydrogenase mutation as a therapeutic target in gliomas. *Chinese Clinical Oncology*, *6*(3), 1–11. <https://doi.org/10.21037/cco.2017.06.11>

- Han, S., Liu, Y., Cai, S. J., Qian, M., Ding, J., Larion, M., Gilbert, M. R., & Yang, C. (2020). IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. *British Journal of Cancer*, *122*(11), 1580–1589. <https://doi.org/10.1038/s41416-020-0814-x>
- Hikmawanti, N. P. E., Hariyanti, H., Nurkamalia, N., & Nurhidayah, S. (2019). Chemical Components of *Ocimum basilicum* L. and *Ocimum tenuiflorum* L. Stem Essential Oils and Evaluation of Their Antioxidant Activities Using DPPH Method. *Pharmaceutical Sciences and Research*, *6*(3), 149–154. <https://doi.org/10.7454/psr.v6i3.4576>
- Kasicki, M. B., & Bagdatlioglu, N. (2016). Bioavailability of quercetin. *Current Research in Nutrition and Food Science*, *4*(SpecialIssue2), 146–151. <https://doi.org/10.12944/CRNFSJ.4.Special-Issue-October.20>
- Kayabolen, A., Yilmaz, E., & Bagci-Onder, T. (2021). IDH mutations in glioma: Double-edged sword in clinical applications? *Biomedicines*, *9*(7). <https://doi.org/10.3390/biomedicines9070799>
- Kolina, J., Sumiwi, S. A., & Levita, J. (2019). MODE IKATAN METABOLIT SEKUNDER DI TANAMAN AKAR KUNING (*Arcangelisia flava* L.) DENGAN NITRAT OKSIDA SINTASE. *FITOFARMAKA: Jurnal Ilmiah Farmasi*, *8*(1), 45–52. <https://doi.org/10.33751/jf.v8i1.1171>
- Liu, Q., Chen, Y., Shen, C., Xiao, Y., Wang, Y., Liu, Z., & Liu, X. (2017). Chicoric acid supplementation prevents systemic inflammation-induced memory impairment and amyloidogenesis via inhibition of NF- $\kappa$ B. *FASEB Journal*, *31*(4), 1494–1507. <https://doi.org/10.1096/fj.201601071R>
- Liu, Y., Tang, Z. G., Lin, Y., Qu, X. G., Lv, W., Wang, G. Bin, & Li, C. L. (2017). Effects of quercetin on proliferation and migration of human glioblastoma U251 cells. *Biomedicine and Pharmacotherapy*, *92*, 33–38. <https://doi.org/10.1016/j.biopha.2017.05.044>
- Lotfi, N., Yousefi, Z., Golabi, M., Khalilian, P., Ghezelbash, B., Montazeri, M., Shams, M. H., Baghbadorani, P. Z., & Eskandari, N. (2023). The potential anti-cancer effects of quercetin on blood, prostate and lung cancers: An update. *Frontiers in Immunology*, *14*(February), 1–21. <https://doi.org/10.3389/fimmu.2023.1077531>
- Mckenney, A. S., Levine, R. L., Mckenney, A. S., & Levine, R. L. (2013). *Isocitrate dehydrogenase mutations in leukemia Find the latest version : Review series Isocitrate dehydrogenase mutations in leukemia*. *123*(9), 3672–3677. <https://doi.org/10.1172/JCI67266.3672>
- Mertens-Talcott, S. U., Talcott, S. T., & Percival, S. S. (2003). Low concentrations of quercetin and ellagic acid synergistically influence proliferation, cytotoxicity and apoptosis in MOLT-4 human leukemia cells. *Journal of Nutrition*, *133*(8), 2669–2674. <https://doi.org/10.1093/jn/133.8.2669>
- Nursamsiar, Toding, A. T., & Awaluddin, A. (2016). Studi In Silico Senyawa Turunan Analog Kalkon Dan Pirimidin Sebagai Antiinflamasi: Prediksi Absorpsi, Distribusi, dan Toksisitas. *Pharmacy*, *13*(01), 92–100.
- Özevren, H., Deveci, E., & Tuncer, M. C. (2020). The effect of rosmarinic acid on deformities occurring in brain tissue by craniectomy method. Histopathological evaluation of iba-1 and gfap expressions. *Acta Cirurgica Brasileira*, *35*(4), 1–10. <https://doi.org/10.1590/s0102-865020200040000006>
- Pandey, P., Khan, F., Qari, H. A., & Oves, M. (2021). Rutin (Bioflavonoid) as cell signaling pathway modulator: Prospects in treatment and chemoprevention. *Pharmaceuticals*, *14*(11). <https://doi.org/10.3390/ph14111069>
- Pantsar, T., & Poso, A. (2018). Binding affinity via docking: Fact and fiction. *Molecules*, *23*(8), 1DUMMY.

- <https://doi.org/10.3390/molecules23081899>
- Perna, S., Alawadhi, H., Riva, A., Allegrini, P., Petrangolini, G., Gasparri, C., Alalwan, T. A., & Rondanelli, M. (2022). *In Vitro and In Vivo Anticancer Activity of Basil (Ocimum spp.): Current Insights and Future Prospects*.
- Prasetiawati, R., Suherman, M., Permana, B., & Rahmawati, R. (2021). Molecular Docking Study of Anthocyanidin Compounds Against Epidermal Growth Factor Receptor (EGFR) as Anti-Lung Cancer. *Indonesian Journal of Pharmaceutical Science and Technology*, 8(1), 8. <https://doi.org/10.24198/ijpst.v8i1.29872>
- Rezzoug, M., Bakchiche, B., Gherib, A., Roberta, A., Guido, F., Kiliñarslan, Ö., Mammadov, R., & Bardaweel, S. K. (2019). Chemical composition and bioactivity of essential oils and Ethanolic extracts of *Ocimum basilicum* L. and *Thymus algeriensis* Boiss. & Reut. from the Algerian Saharan Atlas. *BMC Complementary and Alternative Medicine*, 19(1), 1–10. <https://doi.org/10.1186/s12906-019-2556-y>
- Suárez-Castro, A., Valle-Sánchez, M., Cortés-García, C. J., & Chacón-García, L. (2018). Molecular Docking in Halogen Bonding. *Molecular Docking*. <https://doi.org/10.5772/intechopen.72994>
- Syahputra, G., Ambarsari L., & T, S. (2014). Simulasi docking kurkumin enol, bisdemetoksikurkumin dan analognya sebagai inhibitor enzim 12-lipoksigenase. *Biofisika*, 10(1), 55–67.
- Vitro, I., Vivo, I., Approaches, I. S., Navarrete-vazquez, G., Adolfo, A., Hidalgo-figueroa, S., Isolina, T., S, J. C., & Victor, Y. (2020). *Toxicological Screening of Four Bioactive Citroflavonoids*: 1–12.
- Wang, J., Li, G., Rui, T., Kang, A., Li, G., Fu, T., Li, J., Di, L., & Cai, B. (2017). Pharmacokinetics of rosmarinic acid in rats by LC-MS/MS: absolute bioavailability and dose proportionality. *RSC Advances*, 7(15), 9057–9063. <https://doi.org/10.1039/c6ra28237g>
- Wisbeck, E., Facchini, J. M., Alves, E. P., & Marcia, L. L. (2020). *A polysaccharide fraction extracted from Pleurotus ostreatus mycelial biomass inhibit Sarcoma 180 tumor*. 89(2017), 2013–2020.
- Wootisin, N., Sukprasert, S., Kulsirirat, T., Tharavanij, T., & Sathirakul, K. (2022). Evaluation of the Intestinal Permeability of Rosmarinic Acid from *Thunbergia laurifolia* Leaf Water Extract in a Caco-2 Cell Model. *Molecules*, 27(12). <https://doi.org/10.3390/molecules27123884>
- Wu, C. H., Lin, M. C., Wang, H. C., Yang, M. Y., Jou, M. J., & Wang, C. J. (2011). Rutin Inhibits Oleic Acid Induced Lipid Accumulation via Reducing Lipogenesis and Oxidative Stress in Hepatocarcinoma Cells. *Journal of Food Science*, 76(2), T65–T72. <https://doi.org/10.1111/j.1750-3841.2010.02033.x>
- Xiong, G., Wu, Z., Yi, J., Fu, L., Yang, Z., Hsieh, C., Yin, M., Zeng, X., Wu, C., Lu, A., Chen, X., Hou, T., & Cao, D. (2021). ADMETlab 2.0: An integrated online platform for accurate and comprehensive predictions of ADMET properties. *Nucleic Acids Research*, 49(W1), W5–W14. <https://doi.org/10.1093/nar/gkab255>
- Yi, F. X., Ma, J., Ni, W. M., Chang, R., Liu, W. Da, Han, X. Bin, Pan, D. X., Liu, X. B., & Qiu, J. W. (2013). The top cited articles on glioma stem cells in Web of Science. *Neural Regeneration Research*, 8(15), 1431–1438. <https://doi.org/10.3969/j.issn.1673-5374.2013.15.011>
- Zarlaha, A., Kourkoumelis, N., Stanojkovic, T. P., & Kovala-Demertzi, D. (2014). Cytotoxic activity of essential oil and extracts of *Ocimum Basilicum* against human carcinoma cells. Molecular docking study of isoeugenol as a potent cox and lox inhibitor. *Digest Journal of Nanomaterials and Biostructures*, 9(3), 907–917.
- Ziemska, J., Solecka, J., & Jarończyk, M.

(2020). In silico screening for novel leucine aminopeptidase inhibitors with 3,4-dihydroisoquinoline scaffold. *Molecules*, 25(7).  
<https://doi.org/10.3390/molecules25071753>

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

## ORIGINALITY REPORT

14%

SIMILARITY INDEX

9%

INTERNET SOURCES

10%

PUBLICATIONS

3%

STUDENT PAPERS

## PRIMARY SOURCES

1	<a href="#">biomed.news</a> Internet Source	1%
2	Pratibha Pandey, Fahad Khan, Huda A. Qari, Mohammad Oves. "Rutin (Bioflavonoid) as Cell Signaling Pathway Modulator: Prospects in Treatment and Chemoprevention", Pharmaceuticals, 2021 Publication	1%
3	<a href="#">www.frontiersin.org</a> Internet Source	1%
4	<a href="#">pharmacologyonline.silae.it</a> Internet Source	1%
5	<a href="#">link.springer.com</a> Internet Source	1%
6	<a href="#">mafiadoc.com</a> Internet Source	1%
7	K E Yen. "Cancer-associated IDH mutations: biomarker and therapeutic opportunities",	1%

---

8	Nanthakarn Woottisin, Sophida Sukprasert, Thitianan Kulsirirat, Thipaporn Tharavanij, Korbtham Sathirakul. "Evaluation of the Intestinal Permeability of Rosmarinic Acid from Thunbergia laurifolia Leaf Water Extract in a Caco-2 Cell Model", <i>Molecules</i> , 2022 Publication	1 %
9	<a href="http://www.kspbtjpb.org">www.kspbtjpb.org</a> Internet Source	1 %
10	<a href="http://jddtonline.info">jddtonline.info</a> Internet Source	1 %
11	Submitted to Philippine Council for Health Research and Development Student Paper	1 %
12	Feixiong Cheng, Weihua Li, Yadi Zhou, Jie Shen, Zengrui Wu, Guixia Liu, Philip W. Lee, Yun Tang. "admetSAR: A Comprehensive Source and Free Tool for Assessment of Chemical ADMET Properties", <i>Journal of Chemical Information and Modeling</i> , 2012 Publication	1 %
13	<a href="http://ojs3.unpatti.ac.id">ojs3.unpatti.ac.id</a> Internet Source	1 %
14	Harimurti, Sabtanti, Anisa Ur Rahmah, Abdul Aziz Omar, and Thanapalan Murugesan.	<1 %

"UV/H<sub>2</sub>O<sub>2</sub> Process for Removal of Total Organic Carbon from Refinery Effluent: Screening of Influence Factors Using Response Surface Methodology", Advanced Materials Research, 2014.

Publication

---

15

Chenxing Wu, Hongwang Song, Xiaojun Fu, Shouwei Li, Tao Jiang. "Transcriptomic Analysis of Glioma Based on IDH Status Identifies ACAA2 as a Prognostic Factor in Lower Grade Glioma", BioMed Research International, 2020

Publication

---

<1 %

16

[jrk.fmipa.unand.ac.id](http://jrk.fmipa.unand.ac.id)

Internet Source

---

<1 %

17

Submitted to Centre College

Student Paper

---

<1 %

18

Mohamad Endy Yulianto, Ari Yuniastuti, Dadan Rohdiana, Vita Paramita et al. "Characterization in silico of bioactive compound in tea plant as a potentials inhibitor of SARS-CoV-2 Mpro", Journal of Applied Pharmaceutical Science, 2022

Publication

---

<1 %

19

Alexander Mehring, Ahmed Zayed, Mohamed A. Salem, Saleh Alseekh, Alisdair R. Fernie, Roland Ulber. "Time-dependent behaviour of

<1 %

methyl jasmonate elicited cell suspension cultures of *Ocimum* species via untargeted mass spectrometry-based metabolomics", *Industrial Crops and Products*, 2022

Publication

---

20

Simone Perna, Hajar Alawadhi, Antonella Riva, Pietro Allegrini et al. "In Vitro and In Vivo Anticancer Activity of Basil (*Ocimum* spp.): Current Insights and Future Prospects", *Cancers*, 2022

<1 %

Publication

---

21

I. Bettaieb Rebey, S. Bourgou, W. Aidi Wannes, I. Hamrouni Selami, M. Saidani Tounsi, B. Marzouk, M.-L. Fauconnier, R. Ksouri. "Comparative assessment of phytochemical profiles and antioxidant properties of Tunisian and Egyptian anise (*L.*) seeds ", *Plant Biosystems - An International Journal Dealing with all Aspects of Plant Biology*, 2017

<1 %

Publication

---

22

Zulfiayu Sapiun, Nur'airin Achmadi, Arlan K. Imran, Muindar Muindar et al. "Determination of Sun Protection Factor Lotion of Pulai Stem Extract (*Alstonia scholaris* (L.) R.Br)", *Open Access Macedonian Journal of Medical Sciences*, 2022

<1 %

Publication

---

23

[www.biorxiv.org](http://www.biorxiv.org)

Internet Source

<1 %

24

[www.rj-robbins.com](http://www.rj-robbins.com)

Internet Source

<1 %

25

[1library.net](http://1library.net)

Internet Source

<1 %

26

Andreea-Ina Antonescu (Mintas), Florina Miere (Groza), Luminita Fritea, Mariana Ganea et al. "Perspectives on the Combined Effects of *Ocimum basilicum* and *Trifolium pratense* Extracts in Terms of Phytochemical Profile and Pharmacological Effects", *Plants*, 2021

Publication

<1 %

27

Xiang Chen, Peipei Yang, Yue Qiao, Fei Ye, Zhipeng Wang, Mengting Xu, Xiaowang Han, Li Song, Yuehong Wu, Wen-Bin Ou. "Effects of cancer-associated point mutations on the structure, function, and stability of isocitrate dehydrogenase 2", *Scientific Reports*, 2022

Publication

<1 %

28

[jurnal.uns.ac.id](http://jurnal.uns.ac.id)

Internet Source

<1 %

29

[www.diva-portal.org](http://www.diva-portal.org)

Internet Source

<1 %

30

[www.hindawi.com](http://www.hindawi.com)

Internet Source

<1 %

31

Yue Liu, Zhen-Gang Tang, Yi Lin, Xin-Guo Qu, Wei Lv, Guo-Bin Wang, Cai-Li Li. "Effects of quercetin on proliferation and migration of human glioblastoma U251 cells", Biomedicine & Pharmacotherapy, 2017

Publication

<1 %

32

"Essential Oils", Springer Science and Business Media LLC, 2022

Publication

<1 %

33

[etheses.uin-malang.ac.id](http://etheses.uin-malang.ac.id)

Internet Source

<1 %

Exclude quotes On

Exclude matches < 5 words

Exclude bibliography On