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Anticancer Potency of Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate in Kombucha

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Abstract. *Kombucha has an anticancer potency because it has dimethyl 2-(2-hydroxy-2-methoxypropilidine) malonate compound. The research aimed to verify the compound dimethyl 2-(2-hydroxy-2-methoxypropilidine) malonate as an anticancer with the in-silico method, namely the molecular docking approach, drug likeness profile, and ADMET test. The tools used were the PyRx, Discovery Studio Visualizer, Sanjeevini, and pkCSM. The research material consisted of 3D Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate and Epidermal Growth Factor Receptor (EGFR). The analysis showed Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate is safe for consumption and can suppress cancer cells.*

Keywords: *dimethyl 2- (2-Hydroxy-2-Methoxypropilidine) malonate, EGFR, in silico, Kombucha*

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INTRODUCTION

Kombucha is a traditional beverage usually obtained from the fermentation of black or green tea (sweetened with 5–8% of sugar) by a symbiotic microbial consortium, which is mainly composed of acetic acid bacteria (AAB) and osmophilic yeasts (Marsh et al., 2014). Green and black tea have received considerable attention in recent years as functional beverages due to the high amount of functional compounds, several authors reported a wide spectrum of beneficial activities, studies in vitro or in animal models, including antimicrobial activity against foodborne and human pathogens, hepatic detoxification in

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rats, anti-inflammatory, hypocholesterolemic, anti-proliferative, and hypoglycemic activities (Villarreal et al., 2018), and anticancer (Jayabalan et al., 2011).

Based on the report of Gaggia, et al., (2019) that kombucha has antiproliferative activity on HeLa cells (cervical epithelial carcinoma), HT-29 (colon adenocarcinoma), and MCF-7 (adenocarcinoma), through the sulforhodamine B colorimetric test. In another report, Jayabayan et al., (2011) concluded that the ethyl acetate fraction at a concentration of 100 g/ml of black tea-based kombucha contained dimethyl 2-(2-hydroxy-2- methoxypropylidine) malonate was able to exert significant cytotoxic effects on 786-O cells (human renal carcinoma), U2OS (human osteosarcoma), to reduce cell invasion and cell motility in A549 (human lung carcinoma). In order to understand the molecular interactions between 2-(2-hydroxy-2-methoxypropylidine) malonate with cancer cell receptors, and safety, *in silico* test was performed. This is to provide a clear understanding of the potential of the compound 2-(2-hydroxy-2-methoxypropylidine) malonate in suppressing cancer cells.

In silico testing is a computational-based test, wherein the simulation process in which interaction between the test compound and its cellular receptors is carried out (Suryani et al., 2019). Li et al (2015), stated that in silico research has proven good results. This is based on the results of *in silico* through in vitro, amino acid sequence for *in silico* peptide vaccine proved to be effective on immune cells test.

Compound dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate was tested with the epidermal growth factor (EGFR) receptor, which is one of the cell receptors involved in cancer. The EGFR is a receptor associated with cell proliferation (Carpenter & Cohen, 2014). The EGFR is a key role to regulate epithelial tissue development and homeostasis. In the pathological setting, mostly in lung and breast cancer, EGFR has a role as a tumorigenesis trigger (Sigismund et al., 2017). The EGFR belongs to the ErbB family of receptor tyrosine kinases (RTKs) and exerts critical functions in epithelial cell physiology (Schlessinger, 2014; Nair, 2005). It is frequently mutated and/or overexpressed in different types of human cancers and is the target of multiple cancer therapies currently adopted in the clinical practice (Yarden and Pines, 2012; Wulandari et al., 2021).

The in silico method used is molecular docking. The indictor a good molecular docking result is the affinity value (Kurcinski et al., 2015). This shows that there is a strong molecular interaction between the compound dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate and EGFR. The presence of the molecular interaction indicates that the compound dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate plays a role in EGFR so that the compound a is proven to suppress cancer growth. Prior to molecular docking, a drug-likeness analysis and ADMET test were carried out to determine the safety of dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate for consumption.

MATERIALS AND METHODS

Tools

Hardware

The hardware used was ASUSTek Computer Inc. based on windows 10

Software

The software used consists of:

[1]. Sanjeevini (http://www.scfbio-iitd.res.in/Sanjeevini/index.php)

[2]. pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction)

[3]. PyRx - Python Prescription 0.8
[4]. Discovery Studio Visualizer v20.1.0.19295

Materials

[1]. The three-dimensional structure of EGFR was downloaded from the protein database (www.rcsb.org)
[2]. The three-dimensional structure of dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate was downloaded from pubchem (https://pubchem.ncbi.nlm.nih.gov/)

Procedure

Drug-likeness Profile

Analysis of drug-like properties (drug-likeness) was carried out according to the rules Lipinski (Lipinski's rule of five) which states that a compound has properties similar to drugs when the molecular weight of the compound is less than 500 Dalton, log partition coefficient value P less than 5, the number of hydrogen bond donors less than 5, and the number of hydrogen bond acceptors less than 10 (Nusantoro & Fadlan, 2020). The Analysis of drug-likeness used sanjeevini (http://www.scfbio-iitd.res.in/Sanjeevini/index.php)

Pharmacological Analysis (ADMET)

Pharmacology properties evaluated through absorption, distribution, metabolism, excretion, and toxicity (ADMET). According to Pires et al. (2015) the categories of good ADMET test results are as follows: CaCO2 value more than 0.9 (Absorption)
[1]. Blood Brain Barier (LogBB) value more than 3 (Distribution)
[2]. Category "No" of CYP (Metabolism)
[3]. Category “No” of Renal OCT (Organic Cation Transporter) 2 (excretion)
[4]. Category “No” of AMES Toxicity (Toxicity)

Software for the analysis is pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction)

Molecular Docking

[1]. Ligan

Preparation; dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate and ligan native. For the ligand preparation process use pyrex and refers to Suryani (2018).

[2]. Receptor Preparation EGFR

The receptor preparation process refers to Taupiqurrohman et al (2016). Software for the process is discovery studio visualizer and pyrex.

[3]. Docking

For the molecular docking use pyrex and the process refers to Suryani (2018)

[4]. Analysis of Molecular Docking Result

For the analysis result of molecular docking use discovery studio software and the affinity value as reference.

RESULTS AND DISCUSSION

Drug-likeness Profile

Based on table 1. dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate has good characteristics as a drug. All parameters according to the categories set by Lipinski (2004), namely the compound molecular weight of 217 Dalton (less than 500 dalton), log partition coefficient value P of 0 (less than 5), the number of hydrogen bond of 0 (donors less than 5), and the number of hydrogen bond acceptors of 0 (less than 10). Different results were shown by native ligands. In table 1, it can be seen that the native ligand (Control) is not good if used as a drug. The native ligand has a molecular weight of 506 Dalton (more than 500 Dalton), 9 hydrogen bond donors (more than 5) , and the number of hydrogen bond acceptors of 17 (more than 10), although the log p value of -2.06 (less than 0).

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Table 1. Result of drug likeness profile for dimethyl 2-(2-hydroxy-2-methoxypropilidine) malonate

Compound	Mass	Hydrogen Bond Donor	Hydrogen Bond Acceptors	Log P	Molar Refractivity
Ligan Native (Control)	506.00	9	17	-2.06	97.53
dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate	217.00	0	0	0.00	0.00

Pharmacological Analysis (ADMET)

According to table 2. CaCO2 value for Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate is 1.299, while value of $CaCO_2$ Native Ligan is lower than that, which is -0.806. The $CaCO_2$ parameter is an in vitro model parameter of the intestinal mucosa which is used to predict the absorption of orally administered drugs. The permeability of CaCO2 is high if it has a value of > 0.90 (Harjono, 2017).

Table 2. Result of ADMET analysis for dimethyl 2-(2-hydroxy-2-methoxypropilidine) malonate

Compound	$CaCO_2$	Log BB	CYP	OCT2	Toxicity
Ligan Native (Control)	-0.806	-2.534	No	No	No
Dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate	1.299	-0.203	No	No	No

The CYP and OCT of native ligands were the same as Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate. Prediction process of compounds excretion can be done through the measurement of the total clearance and Renal Organic Caution Transporter 2 (OCT2). Total clearance is a combination of metabolism in the liver and bile, as well as excretion through the kidneys pointed by volume of drug per unit time excreted by the body. This is related to oral bioavailability and determining the dose level in order to achieve a constant concentration (Kriharyani et. al., 2019). Organic Cation Transporter 2 (OCT2) is a transporter in the kidney that plays a role in the disposition and drugs clearance and endogenous compounds. OCT2 substrates have the potential to cause side interactions when given together with OCT2 inhibitors (Pires et al., 2015).

the Log Blood Brain Barrier (BBB/Log B) value for Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate is -0.203, it is greater than native ligan, which is -2.534. Log B is a parameter that serves the ability of drugs to penetrate the blood brain barrier (Rachmania, 2019). This parameter is carried out to reduce side effects and toxicity or can increase the benefits of drugs that have the purpose of treating the brain. A compound can penetrate the brain barrier if it has a LogBB value > 0.3, and cannot penetrate the blood brain barrier if it has a log BB value < -1. According to Roncaglio et al (2013), medicinal compounds that can penetrate the blood brain barrier are compounds that are good for application treatment that targets nerve cells. Compounds that do not target central nervous cells are better cannot penetrate the blood-brain barrier to minimize neurotoxic effects. Based on this explanation, Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate is not suitable for nerve treatment.

Based on the explanation Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate is a good and safe drug for cancer. This is reinforced by the results of the toxicity test ADMET which show nontoxic.

Molecular Docking

The affinity energy value for the molecular docking of the native ligand with EGFR is lower than the affinity energy for Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate with EGFR. It can be seen in table 3 that the affinity energy formed between Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate and EGFR is -4.88, while the native ligand with EGFR is -6.30. However, the molecular interaction between Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) malonate and EGFR is quite strong. This is because the molecular interactions that occur between Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate and EGFR are hydrogen bonds. Hydrogen bonds are the strongest bonds (Arunan et al., 2010).

Figures 1 and 2 show that Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate and the native ligand bind to the appropriate active site of EGFR. Table 4 shows the amino acids of EGFR interacting with Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate, while table 5 describes the interaction between EGFR amino acids and native ligands. Based on table 4, 3 hydrogen bonds and 1 unfavorable bond are formed. While the interaction between the native ligand and EGFR formed 3 electrostatic interactions, 4 hydrogen bonds and 1 unfavorable bond (Table 5). Figures 3 and 4 are visualizations of amino acids from EGFR bound to the test compound Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate and the native ligand. There are 4 amino acids of EGFR bound to Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate, namely Threonin854, Glutamine791, Methionine793, and Methionine793. While in the native ligand there are 6 amino acids, namely Aspartic Acid855, Glutamine762, Leusin762, Leusin788, Lysin745, and Methionine793.

Table 3. Energy affinity

Compound	Binding Affinity (Kcal/mol)
Ligan Native	-6.30
Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Manolat	-4.88

Table 4. Molecular interaction between dimethyl 2-(2-hydroxy-2-methoxypropilidine) malonate with EGFR

Name	Distance	Category	Types	From	From Chemistry	To	To Chemistry
A:THR854:HG1 - :LIG1:O	2.52	Hydrogen Bond	Conventional Hydrogen Bond	A:THR854: HG1	H-Donor	:LIG1:O	H-Acceptor
:LIG1:H - A:GLN791:O	2.80	Hydrogen Bond	Conventional Hydrogen Bond	:LIG1:H	H-Donor	A:GLN791:O	H-Acceptor
:LIG1:C - A:MET793:O	3.61	Hydrogen Bond	Carbon Hydrogen Bond	:LIG1:C	H-Donor	A:MET793:O	H-Acceptor
A:MET793:HN - :LIG1:H	1.29	Unfavorable	Unfavorable Donor-Donor	A:MET793: HN	H-Donor	:LIG1:H	H-Donor

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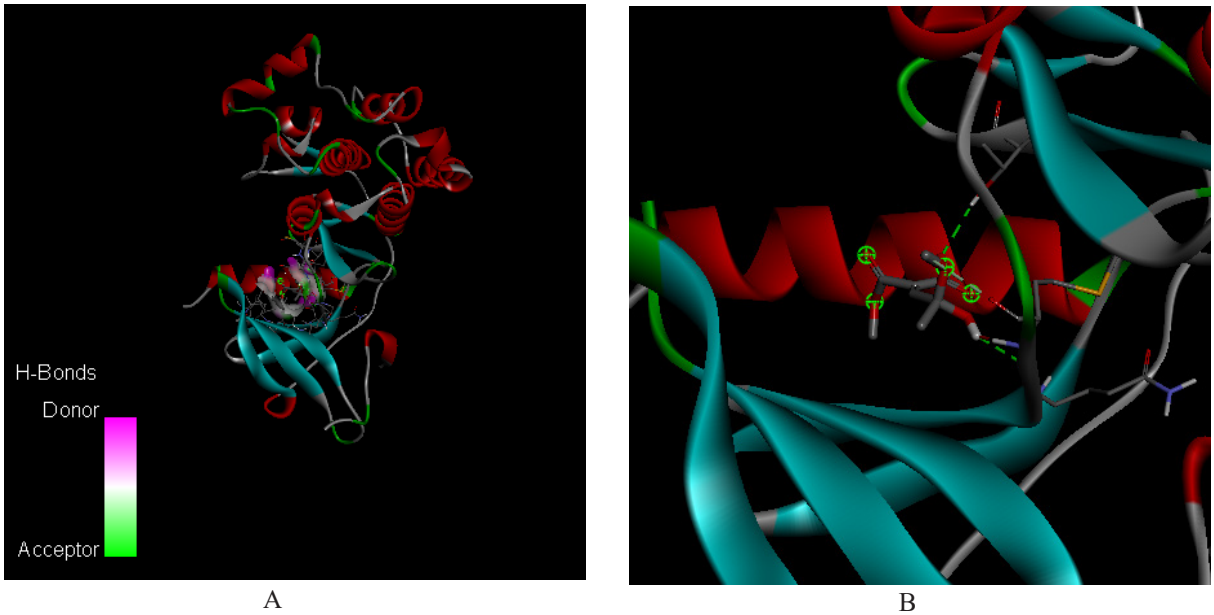
Table 5. Molecular interaction between native ligand with EGFR

Name	Distance	Category	Types	From	From Chemistry	To	To Chemistry
:LIG1:P - A:ASP855:OD2	3.96	Electrostatic	Attractive Charge	:LIG1:P	Positive	A:ASP855: OD2	Negative
:LIG1:P - A:GLU762:OE2	4.67	Electrostatic	Attractive Charge	:LIG1:P	Positive	A:GLU762: OE2	Negative
:LIG1:P - A:ASP855:OD2	3.58	Electrostatic	Attractive Charge	:LIG1:P	Positive	A:ASP855: OD2	Negative
:LIG1:H - A:ASP855:OD2	2.41	Hydrogen Bond	Conventional Hydrogen Bond	:LIG1:H	H-Donor	A:ASP855: OD2	H-Acceptor
:LIG1:HN - :LIG1:O	2.56	Hydrogen Bond	Conventional Hydrogen Bond	:LIG1:HN	H-Donor	:LIG1:O	H-Acceptor
:LIG1:H - A:GLU762: OE2	2.57	Hydrogen Bond	Conventional Hydrogen Bond	:LIG1:H	H-Donor	A:GLU762: OE2	H-Acceptor
:LIG1:C - A:LEU788:O	3.63	Hydrogen Bond	Carbon Hydrogen Bond	:LIG1:C	H-Donor	A:LEU788:O	H-Acceptor
A:LYS745:HZ1 - :LIG1:H	1.39	Unfavorable	Unfavorable Donor-Donor	A:LYS745: HZ1	H-Donor	:LIG1:H	H-Donor
A:MET793:HN - :LIG1:H	2.28	Unfavorable	Unfavorable Donor-Donor	A:MET793: HN	H-Donor	:LIG1:H	H-Donor



A B

Figure 1. Three-Dimensional Visualization of Molecular Docking Results. A. Visualization of The Position of Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonate on The Active Site of EGFR; B. Interaction of The Dimethyl 2-(2-Hydroxy-2-Methoxypropilidine) Malonat with EGFR (enlarged)

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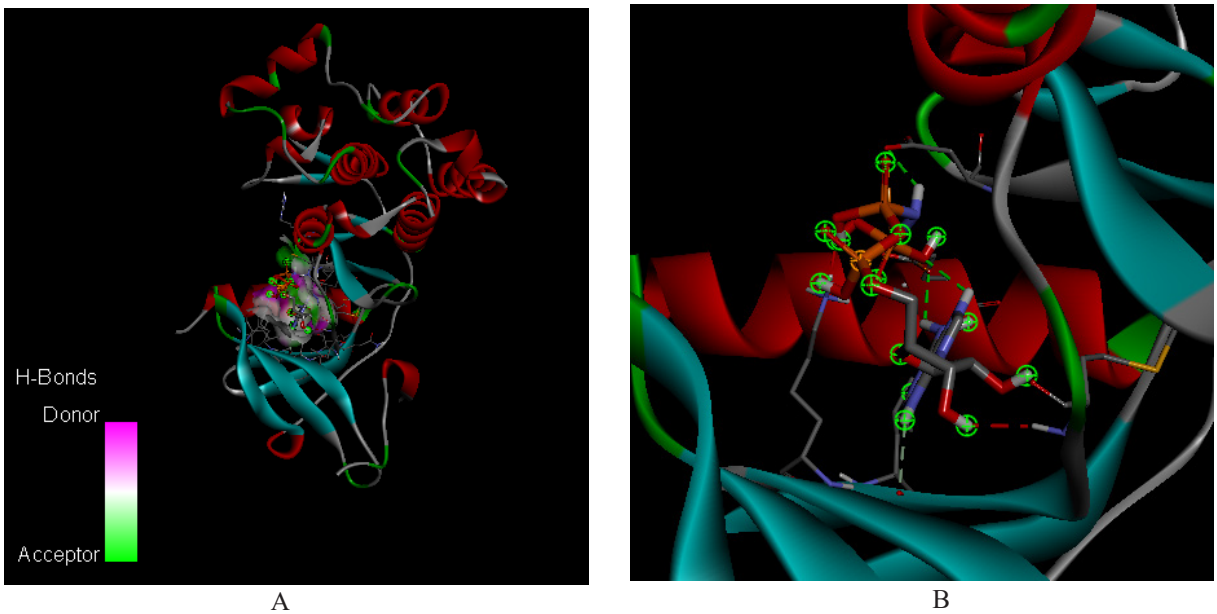

A B

Figure 2. Three-Dimensional Visualization of Molecular Docking Results. A. Visualization of The Position of Ligan Native on The Active Site of EGFR; B. Interaction of The Ligan Native with EGFR (enlarged)

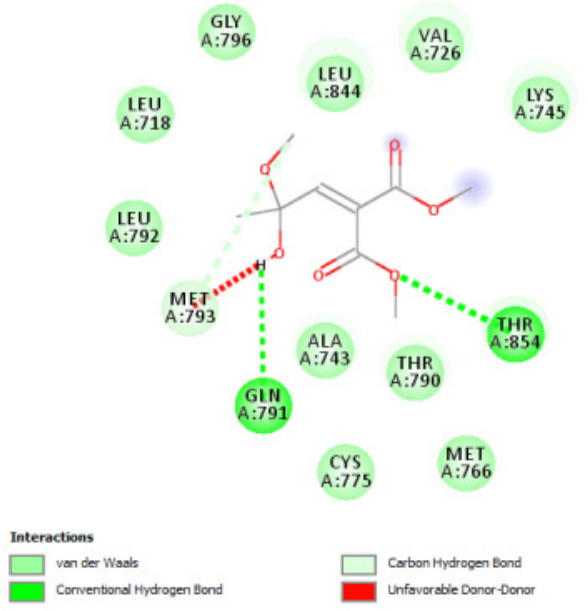

Figure 3. Three-dimensional visualization of molecular interaction between dimethyl 2-(2-hydroxy-2-methoxypropilidine) malonate with EGFRof EGFR; B. Interaction of The Ligan Native with EGFR (enlarged)

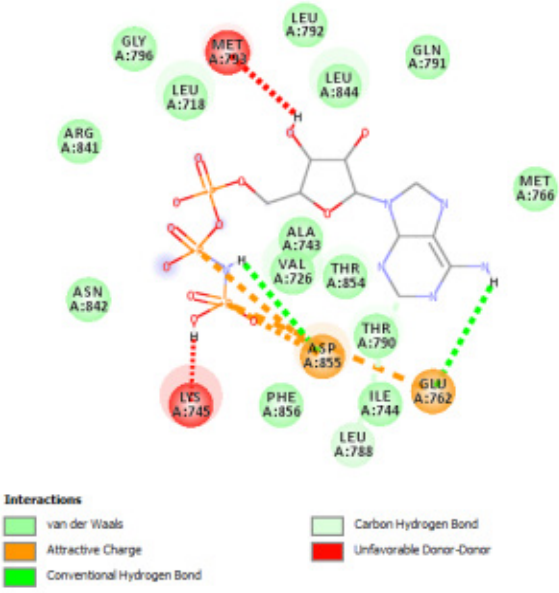

Figure 4. Three dimensional visualization of molecular interaction between of ligan native with EGFR

CONCLUSION

Dimethyl 2-(2-hydroxy-2-methoxypropylidine) malonate was verified as a compound that is safe for consumption and can suppress cancer cells, this is indicated by the fulfillment of all drug likeness and ADMET parameters, as well as the production of low

affinity energy from the molecular docking process.

AUTHOR CONTRIBUTION

O.T. drafting manuscripts, and correcting methods, F.R. propose compounds to be tested, M.F.F. adapted the idea to the method, D.A. customized script layouts with templates and Y.S. adapt introduction, discussion and conclusions based on the results of the review.

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CONFLICT OF INTEREST

The research was conducted without a conflict of interest.

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