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In Silico Studies and Admet Predictions Diterpenoid Compound *Andrographis paniculata* (Burm.f.) Nees as Inhibitor of *Streptococcus mutans*

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ABSTRACT

Andrographis paniculata (Burm.f.) Nees are reported to have many bioactivities, including antibacterial, hepatoprotective, antimalarial, antihypertensive, antipyretic, antithrombolytic, and other pharmacological effects. This study aims to determine the benefits of the active compound *Andrographis paniculata* in inhibiting the activity of the enzyme glucosyltransferase. This research method was carried out in silico on 3AIC receptors using Chimera, ChemDraw Ultra 12.0, MGLtools, Autodock4, Biovia Discovery Studio, and Toxtree software. The results showed that of the 12 test compounds, the AP11 compound has the lowest ΔG free bond energy of -8.5KKal/mol, lower than natural ligands, and more hydrogen bonds than natural ligands, MES. Therefore, it can be concluded that the AP11 compound has the most potential to inhibit glucosyltransferase receptors

Keywords: Sambiloto, In Silico, dental plaque, glukansucrase.

I. INTRODUCTION

Glucosyltransferase (GTF, EC 2.4.1.5) is one of 70 glycoside hydrolase enzymes, as well as a group of sucrase enzymes referred to as glucansucrases or fructansucrases. These enzymes are known to be involved in the synthesis of exopolysaccharides (EPS) from microbes. Exopolysaccharide (EPS) is a polysaccharide produced and excreted from microbes. This EPS has various functions, such as protecting bacterial cells from desiccation, toxic substances, bacteriophages, and osmotic pressure, as well as for biofilm formation (Malik et al. 2018; Anindita 2020). EPS is a biodegradable polymer biosynthesized from various organisms with high molecular weight. EPS is commonly found on the outer structure of prokaryotic and eukaryotic cells. It is associated with the formation of cell capsules or mucus excreted by the cell surface.

EPS exists in a variety of unique and complex chemical structures, provides self-protection against antimicrobial compounds in the environment, and can also be used as carbon and energy reserves (Amanda et al, 2017; Anindita 2020). Glucosucrase catalyzes two different reactions depending on the type of acceptor, namely (i) hydrolysis and (ii) glucosyl group transfer. Glucosyl group transfer can be classified into [a] polymerization and [b] oligosaccharide synthesis. It is called polymerization if the acceptor substrate is a glucan chain, and if the substrate is an oligosaccharide, it is called oligosaccharide synthesis. The accumulation of EPS in teeth can refer to the occurrence of dental caries (Malik et al. 2018; Rachfa et al, 2021). Caries is a disease of the hard tissues of the teeth caused by bacterial fermentation activity. This activity can cause the formation of biofilm (dental plaque). The Dental plaque itself is a deposit of biofilm that is tightly attached to the surface of the teeth and forms when a person is negligent in maintaining dental and oral hygiene (Rahmadina 2020) Dental caries is formed through complex interactions over time between dental plaque, carbohydrate fermentation and host factors (including teeth and saliva). Dental plaque is a thin, colorless layer consisting of a collection of microorganisms that can form at any time (Novita et al, 2015). Biofilms can be a major source of infection by microbes and are difficult to treat due to their resistance to antimicrobials.

Caries is a disease of the hard tissues of the teeth caused by bacterial fermentation activity. This activity can cause the formation of biofilm (dental plaque). The dental plaque itself is a deposit of biofilm that is tightly attached to the surface of the teeth and forms when a person is negligent in maintaining dental and oral hygiene (Rahmadina 2020) Dental caries is formed through complex interactions over time between dental plaque, carbohydrate fermentation and host factors (including teeth and saliva). Dental plaque is a thin, colorless layer, consisting of a collection of microorganisms, that can form at any time (Novita et al, 2015). Biofilms can be a major source of infection by microbes and are difficult to treat because their resistance to antimicrobials is greater than that of individual cells (Purbowati 2016).

S. mutans bacteria play a role in biofilm formation and produce glucosyltransferase enzymes that catalyze biofilm formation (Nurfadillah et al, 2024). This biofilm can be inhabited by a single species or several species of bacteria (Purbowati 2016). S mutans is one of the normal flora bacteria that can cause infections in the oral cavity, are facultative anaerobic, Gram-positive, nonmotile, catalase-negative, β-hemolytic and aciduric bacteria

(Lemos et al. 2019; Nurfadillah et al. 2022). S. mutans has an important role in plaque formation, where these bacteria play a role in the process of forming initial plaque colonies by forming biofilms and producing various surface proteins that coordinate to produce dental plaque, thus inducing dental caries (Friedman 2011; Maghfirah et al. 2017).

S mutans is a cariogenic bacterium that has an important role in the pathogenesis of dental caries (Rachfa et al. 2021). In the process of dental plaque formation, S. mutans produces the enzyme glucosyltransferase. The enzyme can convert sucrose into glucose and fructose and then form glucans or extracellular polysaccharides (EPS) (Zhang et al. 2021). GTF can interact with salivary components such as amylase, which can inhibit the remineralization process in teeth. GTF can also synthesize sucrose EPS to produce glucan which is sticky, helping the adhesion and accumulation of bacteria on the tooth surface and forming a self-defense matrix (Kriswandini et al, 2019; Rachfa et al. 2021). EPS is divided into two groups, namely heteropolysaccharides (composed of glucose, galactose and rhamnose) and homopolysaccharides (glucose or fructose) (Meng et al. 2016). There are 3 types of glucosyltransferase enzymes produced by S. mutans, namely GtfB (gtfB), GtfC (gtfC), and GtfD (gtfD). These three types of enzymes play an important role in the attachment and virulence of S. mutans on the tooth surface (Endriani et al. 2021).

Medicinal plants have become an alternative treatment for several diseases by local communities (Mardiana & Indradi 2020). The utilization of plants that are believed to have medicinal properties in the community continues to grow and is passed down from generation to generation. One of the herbal plants that is believed to have medicinal properties is Andrographis paniculata (Burm.f.) Nees. This plant is one of the medicinal plants that is a top priority to be developed in Indonesia because it contains active compounds, namely andrographolides (diterpene lactones), flavonoids, quinic acid, steroids, alkaloids, saponins, tannins, etc. With a variety of compounds, A. paniculata is one of the most popular medicinal plants in Indonesia. With a variety of compounds, A paniculata (Burm.f.) Nees has various pharmacological activities, including antibacterial, antiviral, antibiofilm, antifungal, antimalarial, anti-inflammatory, platelet anti-aggregation, antidiabetic, and has a role in improving the immune system (Royani et al, 2014; Gede et al. 2022). Therefore, researchers are interested in exploring the benefits of various plant compounds A paniculata (Burm.f.) Nees in inhibiting the growth of S mutans.

II. MATERIAL AND METHODS

The research was conducted using a Lenovo IdeaCentre AIO 3 24IAP7-Type FOGH PC device with 12th generation Intel® Core i3-1215U processor, 8 GB DDR4 3200 Memory, 512 GB SSD PCIe Hard Drive. The software used in this research includes Chimera, ChemDraw Ultra 12.0, MGLtools, Autodock4, Biovia Discovery Studio, and Toxtree. The materials used in this study are bioactive compounds of the diterpenoid group of the Andrographis paniculata sambiloto plant obtained from the KnapSack online database and continued by checking the potential of the compound on the PASS Online. Ligands were then minimized using chimeras. Lipinski's Rule of Five prediction was carried out to determine the physicochemical profile of the compound to be tested to determine its ability as an oral drug preparation. The ligands were

analyzed on the SwissADME website. Testing parameters include molecular weight, logP, donor hydrogen bonding, and receptor hydrogen bonding.

The Gtf target protein (code 3AIC) was downloaded on Pubchem and then pretreated using Chimera software by removing water and residual solvents. The docking process was performed using Autodock. Before molecular docking between the receptor and the test ligand, redocking between the receptor and native ligand (MES) was performed. The parameters used are: binding affinity value, binding type, and amino acid residues. The docking results of ligand and receptor were visualized on Biovia Discovery Studio 2021 both in 3D and 2D. ADMET (Adsorption, Distribution, Metabolism, Excretion, Toxicology) analysis was performed to determine the physicochemical profile and toxicity of the test compounds. The analysis was done through the PreADMET website and Toxtree software. Parameters analyzed in this stage include %HIA (Human Intestinal Absorption), Caco2 (Cancer coli-2), PPB (Plasma Protein Binding), BBB (Blood-Brain Barrier) values, as well as toxicity test results with Ames Test, Carcinogenicity, and mutagenic parameters.

III. RESULTS AND DISCUSSION

Glucosyltransferase is an enzyme that plays an important role in the process of bacterial attachment and virulence on the tooth surface. This enzyme is able to break down sucrose into glucose and fructose to form glucan polymers called extracellular polysaccharides (EPS). Inhibition of glucosyltransferase in S. mutans can reduce the incidence of dental caries (Nurfadillah et al, 2023).

The A paniculata plant is a plant that is rich in pharmacological effects, including: It has hepatoprotector, antibiotic, antimalarial, antihypertensive, antipyretic, antithrombolytic, and antidote for snake bites (Cahyawati et al. 2021) These pharmacological effects come from phytochemical compounds contained in plants. Sambiloto contains active compounds, namely andrographolide (diterpenlactone), flavonoids, quinic acid, steroids, alkaloids, saponins, tannins, and other compounds (Hita et al. 2022).

A total of 12 compounds containing A. paniculata were obtained from the Knapsack website. Prediction of compound potential aims to understand the properties and biological activity of these compounds, especially in the context of their use as drugs or natural ingredients. The parameters used are Pa (Potential Activity) and Pi (Potential Inactivity) values. Prediction of the potential of A. paniculata plant compounds is obtained from the way2drug PASS online site. The results of the analysis of the potential of A. paniculata plant compounds as antibacterial can be seen in Table 1.

Table 1. The Pa and Pi values of A. paniculata plant compounds as antibacterials

No	Compound Name/Compound Code	Formula	Pa Value	Pi Value
1	14-deoxy11,12-didehydroandrographolide (AP1)	$C_{20}H_{28}O_4$	0,481	0,018
2	14-deoxy-11,12-dihydroandrographolide (AP2)	$C_{20}H_{28}O_4$	0,432	0,024

3	14-deoxy-11-hydroxyandrographolide (AP3)	$C_{20}H_{30}O_5$	0,532	0,014
4	14-deoxy-11-oxoandrographolide (AP4)	$C_{20}H_{28}O_5$	0,462	0,020
5	14-deoxy-12-methoxyandrographolide (AP5)	$C_{21}H_{32}O_5$	0,485	0,018
6	14-deoxy-15-isopropylidene-11,12 didehydroandrographolide (AP6)	$C_{23}H_{32}O_4$	0,504	0,016
7	14-deoxyandrographolide (AP7)	$C_{20}H_{30}O_4$	0,451	0,022
8	Andrographolactone (AP8)	$C_{20}H_{24}O_2$	0,172	0,143
9	Andrographolide (AP9)	$C_{20}H_{30}O_5$	0,550	0,012
10	Isoandrographolide (AP10)	$C_{20}H_{30}O_5$	0,551	0,012
11	Andrographoside (AP11)	$C_{26}H_{40}O_{10}$	0,709	0,004
12	Neoandrographolide (AP12)	$C_{26}H_{40}O_8$	0,531	0,014

Source: Knapsack and Way2Drug PASS online (2024)

Based on Table 1. It can be seen that the andrographoside compound has a higher Pa value (0.709) than the other 11 compounds. Followed by isoandrographolide (0.551), andrographolide (0.550), 14-deoxy-11-hydroxyandrographolide (0.532), neoandrographolide (0.531), and 14-deoxy-15-isopropylidene-11,12 didehydroandrographolide (0.504). The online PASS test results provide information on Pa (Potential activity) and Pi (Potential inhibitory) values. The PASS test value of Pa > 0.7, means that the compound is very biologically active and the results are not significantly different from laboratory-scale tests. Conversely, if the Pa value is 0.5 < Pa < 0.7, the compound has a fairly high bioactivity, making it a bioactive compound that will show a high chance of success when tested in vitro and or in vivo experimentally (Yasmin et al. 2022)

Table 2. Lipinski Test Results (Rule of Five) for 12 ligand compounds

No	Compound Code	Massa	HBD	HBA	LogP	MR
1	Native ligand	182	0	5	-0.300	35.993
2	AP1	332	2	4	2.767	92.076
3	AP2	332	2	4	2.767	92.076
4	AP3	350	3	5	1.962	93.560
5	AP4	348	2	5	2.170	92.560
6	AP5	364	2	5	2.616	98.350
7	AP6	372	2	4	4.061	105.583
8	AP7	334	2	4	2.991	92.170
9	AP8	296	0	2	4.458	89.867
10	AP9	350	3	5	1.962	93.560
11	AP10	350	2	5	2.203	91.691
12	AP11	512	6	10	-0.213	126.193
13	AP12	480	4	8	1.845	123.414

Source: Lipinski Rule of Five (2024)

The Lipinski test is used to determine the permeability and absorption properties of a molecule or compound. Lipinski test results for 12 test compounds and native ligands can be seen in Table 2. Five parameters in Lipinski RO5 must be met, namely: Mass < 500 D, hydrogen bound donors (HBD) no more than 5, Hydrogen Bound Acceptors (HBA) no more than 10, logP no more than 5, and Molar refractivity between 40 - 130. Based on Table 2, it can be seen that all test compounds have Mass, LogP, and MR values greater than the native ligand. From the 12 test compounds, 11 compounds have met the Lipinski parameters, while AP11 has BM and HBD values greater than the native ligand. Drugs are expected to be able to reach the target so that the active compounds contained in the drug can interact well in the body. Drugs given orally must fulfill these five rules. Otherwise, it is better to be given by injection because it is thought to harm the human body (Maftucha et al. 2022; Fadillah et al 2023).

Ligands and receptors that have been prepared in chimera software are then carried out molecular docking simulations in autodock software. Receptor preparation is done by removing unused chains, water content, residues, and native ligands. Removal of water molecules is done to maximize the interaction between the test ligand and the receptor. Generally, the interaction that occurs between ligands and receptors is in the form of hydrogen bonds, so it is necessary to add hydrogen to optimize the interaction that will occur. Ligand preparation is done by minimizing to make the ligand more stable during the molecular docking process (Nurfadillah et al. 2023).

Table 3. Molecular Docking results of 12 compounds ligands against 3AIC receptor

No	Compound Code	Binding Affinity (Kcal/mol)	RMSD	Amino Acid Residue	Hydrogen Bond	Bond Distance
1	Ligand native	-4.8	0	ASP995 THR1051 ALA963 ASN1052 ASN436 TYR962	THR1051 ALA963 ASN1052 ASN436	3,00 2,98 3,02 3,30
2	AP1	-8.1	0	TYR430 ASP909 ASP588 ASP477 ALA478 LEU433	TYR430 ASP477	3,04 2,83
3	AP2	-8.0	0	TYR610 ASP588 ALA478 LEU433	TYR610	3,13

4	AP3	-7.3	0	ASP477 TYR610 ASP593	ASP477 TYR610	2,11 2,86
5	AP4	-7.7	0	SP588 TYR430 ASP480 GLN592	TYR430	2,97
6	AP5	-6.8	0	LYS948 ARG854 ALA850	LYS948 ARG854	2,44 2,81
7	AP6	-8.4	0	ASP588 LEU433 ALA478 GLY429 ASP480 TRP517	-	-
8	AP7	-7.6	0	LEU433 ALA478 ASP588 ASP477 TYR430	TYR430	3,18
9	AP8	-8.3	0	TYR916 VAL957 ASN481 TYR430 GLU515 ASP588 ALA478 LEU433	ASN481 TYR430	3,25 3,04
10	AP9	-7.8	0	GLN592 ASP588 LEU433 ALA478 ASN481 GLY429	GLN592 ASN481	3,10 2,41
11	AP10	-7.2	0	THR426 TYR430 TYR430	THR426 TYR430 TYR430	2,67 2,87 2,86
12	AP11	-8.5	0	TYR610 TYR430 TRP517 GLN592 ASP588 HIS587 ASP477	TYR610 TYR430 GLN592 HIS587 ASP477 ASP477 GLU515	2,88 3,06 3,02 2,39 2,51 2,35 2,39

				ASP477 GLU515		
13	AP12	-8.3	0	GLN592 HIS587 ARG540 ASN537 TRP517	HIS587 ARG540 ARG540 ASN537	2,65 3,07 3,14 3,22

Source: Primary Data (2024)

The parameters used are: binding affinity, RMSD (Root Mean Square Deviation) value, bond type, amino acid residues formed, and bond distance. The results of molecular docking 12 ligands compounds can be seen in Table 3. Binding affinity is a parameter used to see the strength of interaction between ligand and receptor. From Table 3, it is known that the twelve test compounds have smaller binding affinity values when compared to the native ligand. The smaller the value, the stronger and more stable the bond formed between the ligand and the receptor. Negative values indicate the smallest energy used by the receptor to interact with the ligand, so that the reaction can take place spontaneously (Naufa et al, 2021; Rachmania et al, 2022).

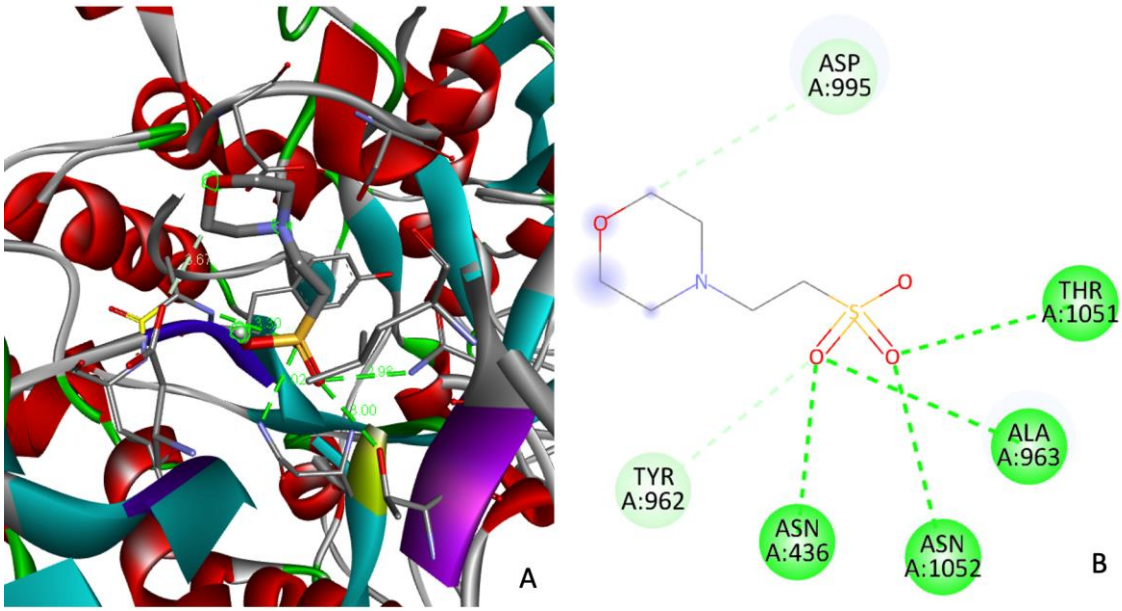

Image 1. Molecular docking simulation (A) Interaction between receptor and AP1 test ligand in 3D showing bond type and bond distance; (B) Interaction between receptor and AP1 test ligand in 2D showing bond type and amino acid residue (Primary Data, 2024)

RMSD value is a parameter used to compare the atomic position between the experimental structure and the predicted structure. Based on Table 3, it can be said that all test compounds have atomic positions that are in accordance with the native ligand because the RMSD value is 0. This is in accordance with the criteria for docking success, which has an RMSD value <2.0Å which indicates that the pose of the native ligand with the docking ligand

is increasingly similar or good because it is close to the conformation of the native ligand (Nurfadillah et al. 2023). Interaksi antara resept(Malik et al. 2018; Anindita 2020).

EPS itself is a biodegradable polymer biosynthesized from various organisms with high molecular weight. EPS is commonly found on the outer structure of prokaryotic and eukaryotic cells. It is associated with the formation of cell capsules or mucus excreted by the cell surface. EPS exists in a variety of unique and complex chemical structures, provides self-protection against antimicrobial compounds in the environment and can also be used as carbon and energy reserves (Amanda et al, 2017; Anindita 2020). Glucosucrase catalyzes two different reactions depending on the type of acceptor, namely (i) hydrolysis and (ii) glucosyl group transfer. Glucosyl group transfer can be classified into: [a] polymerization, and [b] oligosaccharide synthesis. It is called polymerization if the acceptor substrate is a glucan chain, and if the substrate is an oligosaccharide, it is called oligosaccharide synthesis. The accumulation of EPS in teeth can refer to the occurrence of dental caries (Malik et al. 2018; Rachfa et al, 2021).

Caries is a disease of the hard tissues of the teeth caused by bacterial fermentation activity. This activity can cause the formation of biofilm (dental plaque). The dental plaque itself is a deposit of biofilm that is tightly attached to the surface of the teeth and forms when a person is negligent in maintaining dental and oral hygiene (Rahmadina 2020) Dental caries is formed through complex interactions over time between dental plaque, carbohydrate fermentation and host factors (including teeth and saliva). Dental plaque is a thin, colorless layer, consisting of a collection of microorganisms that can form at any time (Novita et al, 2015).

In medicinal chemistry studies, ADMET analysis is used to analyze the ability of drugs to enter cells. ADMET analysis consists of absorption, distribution, metabolism, and toxicity parameters. Absorption parameters consist of HIA (Human Intestinal Absorption) and Caco-2 (Cancer coli-2). The distribution consists of PPB (Plasma Protein Binding) and BBB (Blood Brain Barrier). Metabolism consists of CYP and toxicity seen from mutagens and carcinogens. The HIA value indicates the degree of absorption of the active substance in the human gut. There are three categories, namely HIA 0-20% (low), 20-70% (medium), and 70-100% (high). Based on Table 4, it can be concluded that AP11 is classified as moderate absorption, while the other 11 test compounds are classified as high absorption or can be absorbed well in the human intestine. Prediction of drug absorption by the human gut (HIA%) is very important in the process of developing potential drug compound candidates. Caco-2 cell modeling is recommended in predicting the absorption of orally administered active substances. The uptake quality of Caco-2 cells is categorized into three groups, namely: <4 (low), 4-70 (medium), and >70 (high). Based on Table 4, it can be concluded that the 12 test compounds are considered to have moderate permeability or uptake ability (Lestari et al. 2023).

Good drug distribution requires good BBB and PPB channeling capabilities. Table 4 shows that there are 7 test ligands (AP1, AP2, AP3, AP6, Ap7, AP8, and AP9) that have PPB values >90%, while the remaining 5 (AP4, AP5, AP10, 1P11, and AP12) have PPB values <90%. A %PPB value of more than 90% indicates that the compound is strongly bound to plasma proteins, a drug is more efficient if it is free to cross the plasma membrane and reach

the target than if it binds to plasma proteins. The BBB value can give an idea regarding the permeability of the tested drug across the blood brain barrier. BBB values are divided into 3 based on the strength of absorption, namely: high (>2), medium (2-0.1), and low (<0.1). Based on Table 4, it can be concluded that: 2 test ligands (AP4 and AP11) were not able to cross the brain barrier; 9 test ligands (AP1, AP2, AP3, AP5, AP6, AP7, AP9, and AP12) were moderately able to cross the brain barrier; and 1 test ligand (AP8) was able to cross the brain barrier well. Not all drugs have to cross the blood-brain barrier if the target of the drug is not related to the central nervous system. Prediction of distribution with P-glycoprotein (Pgp) inhibition and substrate parameters is important because P-glycoprotein is one of the drug transporters that determine the absorption and release of various drugs. P-gp plays an important role in regulating drug concentration in plasma and peripheral tissues, which directly affects drug efficacy and toxicity. Toxicity is one of the criteria that needs to be considered in the selection of drug candidates for safe use. The toxicity parameters used are Kroes TTC, mutagens, and carcinogens. Based on Table 4, it can be seen that all 12 test compounds are safe, not mutagens and carcinogens (Elsiana et al. 2023; Klara et al. 2023; Lestari et al. 2023).

Table 4. ADMET analysis results of 12 test ligands

		Absorption		Distribution			Toxicity		
No	**Compound Code**	**Caco2**	**HIA**	**PPB**	**BBB**	**Pgp inhibition**	**Kroes TTC**	**Carcinogen**	**Mutagen**
1	AP1	20.60	92.95	98.43	0,34	Inhibitor	Safe	-	-
2	AP2	20.24	92.67	91.13	0,30	inhibitor	Safe	-	-
3	AP3	19.97	86.60	90.03	0,17	non	Safe	-	-
4	AP4	19.01	91.92	88.14	0,05	non	Safe	-	-
5	AP5	21.80	93.04	88.30	0,17	non	Safe	-	-
6	AP6	22.11	93.75	98.92	1,22	inhibitor	Safe	-	-
7	AP7	20.61	92.67	100	0,48	inhibitor	Safe	-	-
8	AP8	37.88	100.00	100	8,55	inhibitor	Safe	-	-
9	AP9	18.67	88.35	96.95	0,23	non	Safe	-	-
10	AP10	15.56	91.74	75.06	0,10	non	Safe	-	-
11	AP11	16.88	40.18	63.90	0,04	non	Safe	-	-
12	AP12	19.00	80.78	89.59	0,12	inhibitor	Safe	-	-

Sumber: Preadmet; Toxtree (2024)

IV. CONCLUSION

Based on the analysis that has been done, it can be concluded that the AP11 compound is the most potential compound in S. mutans (glucosyltransferase) inhibition.

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