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MOLECULAR DOCKING STUDIES ON ANTI-DIABETIC PROPERTIES OF PROPOLIS FROM STINGLESS BEE (*Tetragonula biroi* Friese)

Adonis A. Yanos[1*], Raphael Angelo Z. Gonzales[1], Paul Lloydson J. Alvarez[1,2] and Mark Rickard N. Angelia[1,2]

[1]Institute of Chemistry, College of Arts and Sciences, University of the Philippines Los Baños, College, Laguna, Philippines
[2]UPLB Bee Program
*Corresponding author: aayanos@up.edu.ph

ABSTRACT

Diabetes mellitus is one of the leading causes of mortality among non-communicable diseases. The Philippines is reported to be one of the countries with high cases of diabetes mellitus. As such, there exists a need to improve current anti-diabetic drugs into safer, more accessible, and cheaper models. In this study, the potential anti-diabetic properties of compounds present in stingless bee propolis (apigenin, artepillin C, luteolin-5-methyl ether, pinobanksin-3-O-butyrate, pinobanksin-5,7-dimethyl ether, and pinocembrin-5-methyl ether) were screened through molecular docking. The relative binding affinities of the tested compounds against pre-defined binding sites in several diabetes-relevant enzymes was determined. For 11β-hydroxysteroid dehydrogenase type 1, pinobanksin-3-O-butyrate had the best binding energy score of -9.2±0.1 kcal/mol. For aldose reductase, both apigenin and luteolin-5-methyl ether had the best binding energy score of -9.7±0.0 kcal/mol and -9.7±0.1 kcal/mol, respectively. For glutamine: fructose-6-phosphate amidotransferase, both luteolin-5-methyl ether and pinobanksin-3-O-butyrate had the best binding energy score of -7.8±0.1 kcal/mol and -7.8±0.0 kcal/mol, respectively. For glucokinase, apigenin had the best binding energy score of -8.6±0.1 kcal/mol. For N-terminal maltase glucoamylase, artepillin C had the best binding energy score of -7.6±0.0 kcal/mol. And lastly for human pancreatic α-amylase, luteolin-5-methyl ether had the best binding energy score of -9.6±0.1 kcal/mol. After docking, the ADMET properties (absorption, distribution, metabolism, excretion and toxicity) were determined using SwissADME. In terms of the ADMET properties, pinobanksin-3-O-butyrate showed the highest potential for drug development.

Key words: anti-diabetic drugs, diabetes mellitus, molecular docking, propolis, stingless bee

INTRODUCTION

Propolis, also known as bee glue, is a sticky resinous substance produced by bees. It serves to maintain structural integrity of the hive. It is utilized to protect the larvae, due to its antiseptic and antimicrobial action (Anjum et al., 2019). This bioactivity is due to propolis being sourced from a variety of plants, trees, and other flora, which contain a breadth of phytochemicals with different activities. Mostly, the substance consists of phenolics—flavonoids and phenolic acids—while other notable compounds include waxes, volatiles, minerals, and pollen residues (Farooqui & Farooqui, 2012). These compounds have been found

to exhibit antioxidant, anti-inflammatory, anti-tumor, anti-ulcer, anti-cancer, and antidiabetic activities (Sforcin & Bankova, 2011). Thus, propolis has found a variety of uses. It is present in dietary supplements, lotions, and antiseptics, for a few examples.

Diabetes mellitus (DM) are of 2 types (American Diabetes Association, 2014): DM that involves the breakdown of pancreatic β-cells in the system, which leads to an absolute loss of insulin (type 1) and DM that is due to insulin resistance due to unresponsiveness of target tissues (type 2). Recently, several pharmacological approaches have been studied for use in DM treatment such as 11β-hydroxysteroid dehydrogenase 1 inhibitors (Almeida et al., 2021), aldose reductase inhibitors (Jannapureddy et al., 2021), glutamine:fructose-6-phosphate amidotransferase inhibitors (Nakaishi et al., 2009), N-terminal maltase-glucoamylase inhibitors (Sim et al., 2010), pancreatic α-amylase inhibitors (Dandekar et al., 2021), glucokinase activators (Kamata et al., 2004) and many others. Diabetes mellitus is one of the leading causes of mortality among non-communicable diseases. Even the Philippines is not exempted to the problem. It is estimated that by 2030, Philippines will be among the top ten countries with the most cases of diabetes mellitus (Wild et al., 2004). As such, there exists a need to improve current anti-diabetic drugs into safer, more accessible, and cheaper models.

Promising progress may be found in exploring stingless bee propolis compounds for their anti-diabetic properties through molecular docking. In the Philippines, *Tetragonula biroi* (Friese) is the most common species. Alvarez et al. (2013) have identified six flavonoids and phenolic compounds from *T. biroi* propolis (apigenin, artepillin C, luteolin-5-methyl ether, pinobanksin-3-O-butyrate, pinobanksin-5,7-dimethyl ether, and pinocembrin-5-methyl ether) using LCMS analysis. Flavonoids and phenolic compounds have been reported to have biological activities such as antioxidant, anti-inflammatory, and anti-diabetic activities. However, the bioactivity of *T. biroi* propolis still has not been extensively studied in comparison to propolis from other countries. The goal of this study, then, is to utilize molecular docking to screen the six compounds present in *T. biroi* propolis for their binding affinity towards various diabetes-related enzymes and to predict their probability for eventual drug development.

MATERIALS AND METHODS

Ligand Preparation

Alvarez et al. (2013) have identified six compounds from *T. biroi* propolis using LCMS analysis. All of these compounds were used as ligands in this study. The spatial data file (SDF) of the compounds (apigenin, artepillin C, luteolin-5-methyl ether) was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov). Compounds with no existing SDF files in PubChem (pinobanksin-3-O-butyrate, pinobanksin-5,7-dimethyl ether, pinocembrin-5-methyl ether) were manually

drawn in Avogadro version 1.2.0 and their 3D geometries were optimized using the same software (Hanwell et al., 2012). Gasteiger charges and non-polar hydrogens were added to the ligand and the number of torsions were determined using AutoDock Tools v1.5.6 (Morris et al., 2009).

Receptors Preparation

The crystal structure of various diabetes-related enzymes – 11β-hydroxysteroid dehydrogenase 1 (PID: 4K1L), aldose reductase (PID: 3G5E), glutamine:fructose-6-phosphate amidotransferase (PID: 2ZJ4), glucokinase (PID: 1V4S), N-terminal maltase gluco-amylase (PID: 2QMJ), and human pancreatic α-amylase (PID: 3BAJ) – were retrieved from Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (http://www.rcsb.org). Downloaded files were opened using BIOVIA Discovery Studio Visualizer 2021 wherein water molecules and ligands attached to the receptors were removed. Polar hydrogens and Kollman charges were added using AutoDock Tools v1.5.6 (Morris et al., 2009).

Molecular Docking

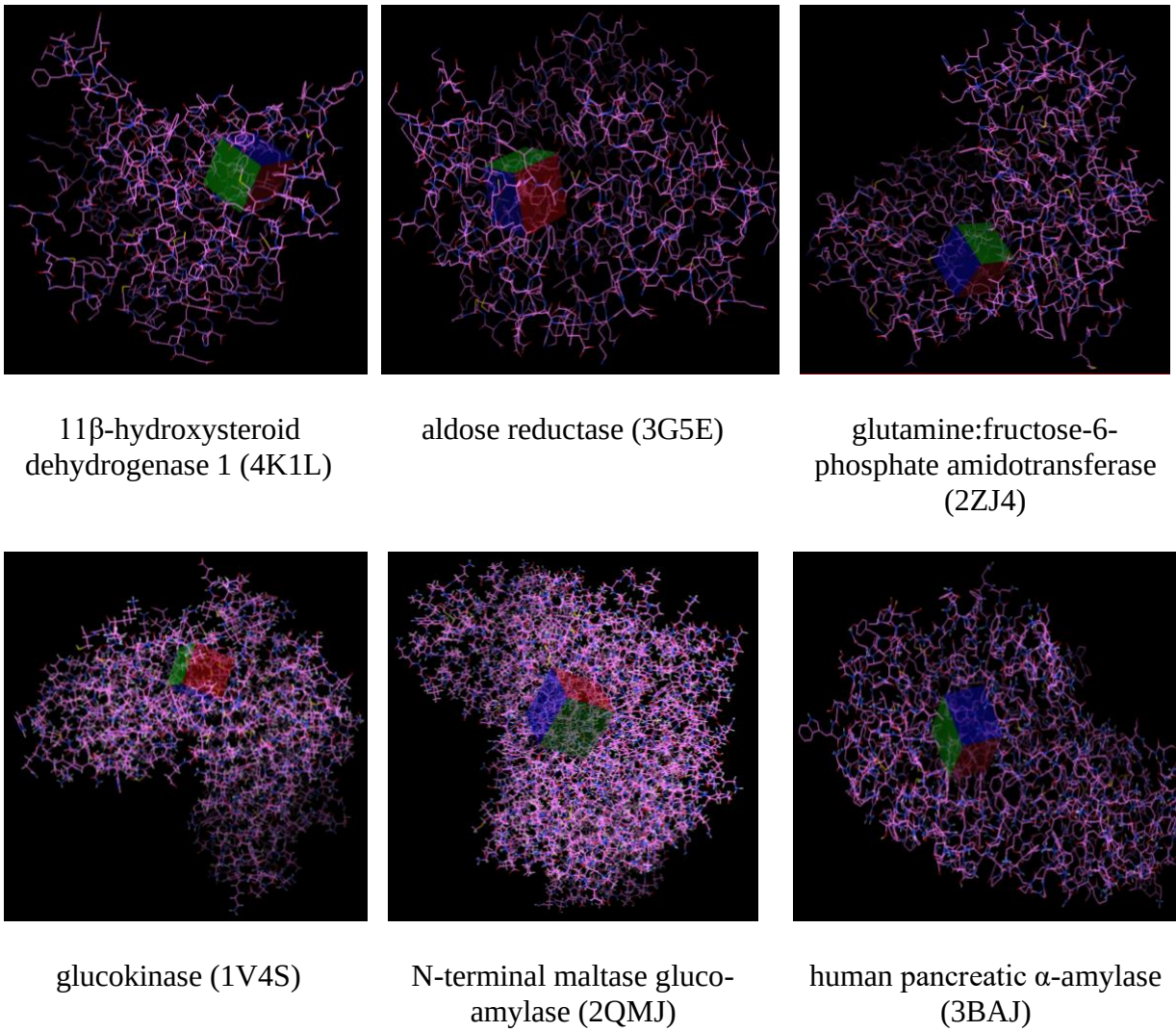
The Protein Data Bank, Partial Charge, and Atom Type (PDBQT) files of the ligands and receptors were generated using AutoDock Tools v1.5.6 (Morris et al., 2009). The same software was used to ensure that the grids were centered on and fully cover predetermined binding sites in the different enzymes. These binding sites were obtained from the top docks of a previously performed blind docking. The grid box used for each receptor are shown in **Figure 1**. Molecular docking simulations were carried out using AutoDock Vina. The docking simulations follows the rigid receptor-flexible ligand format. This kind of docking trades the higher accuracy of a flexible receptor for the lower computing time provided by a rigid receptor (Meng et al., 2011). All docking simulations were done in triplicate.

Analysis and Visualization

For each docking simulation, the binding conformation with the most negative binding energy score was considered for further analysis. The interactions between the receptors and ligands were identified using BIOVIA Discovery Studio Visualizer 2021.

Lead- and Drug-likeness Properties

ADMET properties of the ligands were determined using SwissADME (Daina et al., 2017). The structure of each ligand was entered at the interface of the website (https://swissadme.ch/). These ADMET properties were used to predict the probability of the ligands for eventual drug development.



11β-hydroxysteroid dehydrogenase 1 (4K1L) | aldose reductase (3G5E) | glutamine:fructose-6-phosphate amidotransferase (2ZJ4)

glucokinase (1V4S) | N-terminal maltase gluco-amylase (2QMJ) | human pancreatic α-amylase (3BAJ)

Figure 1. Grid box used in molecular docking to the various diabetes-related enzymes.

RESULTS AND DISCUSSION

According to Kitamura (2019), various studies on different animal and cellular models indicated that propolis modulates oxidative stress, the accumulation of advanced glycation end products, and adipose tissue inflammation (all are related to insulin resistance or defective insulin secretion). Some studies focused on α-glucosidase inhibition such as the propolis from Indonesian stingless bees (Pujirahayu et al., 2019), Okinawa propolis (Shahinozzaman et al., 2018) and compounds isolated from Thai stingless bees in a mangosteen orchard (Vongsak et al., 2015). Meanwhile, the anti-diabetic activity of Malaysian soft propolis from *Heterotrigona itama* has also been explored and paired with metformin in a study by Nna et al. (2018). The study concluded that it can act synergistically with metformin in reducing blood

glucose and repairing pancreatic β-cells. On the other hand, Zhu et al. (2011) studied Chinese and Brazilian propolis and found that both inhibited body weight loss and blood glucose increase in diabetic rats. Furthermore, oxidative stress in the blood, liver, kidney was significantly reduced. As such, they believe that Chinese and Brazilian propolis can alleviate diabetes symptoms as well, due to the antioxidant properties of the bioactive compounds present. Based on these results, this study was directed to determine the anti-diabetic properties of the compounds present in *T. biroi* propolis for their binding activity towards various diabetes-related enzymes using a molecular docking approach.

In this study, six *T. biroi* propolis compounds were docked to six different diabetes-related enzymes. Each of the docking simulation returned 9 ligand-receptor docking results. The range of predicted binding energy scores for all the docking results are summarized in **Table 1**. Moreover, the location of all the docked ligands for each of the receptors are shown in **Figure 2**. These results show that all the ligands have a good binding affinity towards the binding site of each receptor since all showed similar values to that of the control. In molecular docking, the docked ligand with a more negative binding energy score is considered to have stronger binding towards the receptor (Sailah et al., 2021). The binding energy score of each of the docking simulations are summarized in **Table 2** as well as the binding energy score of the control used for each receptor.

The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is responsible for the conversion of cortisone to cortisol, which play important role in enhancing glucose production, regulating gluconeogenesis, and inhibiting glucose uptake (Almeida et al., 2021). The control used was carbenoxolone which is a steroidal derivative of glycyrrhettinic acid that has been investigated to inhibit 11β-HSD1. None of the propolis compounds exceeded the binding energy score of this control which is -9.3±0.0 kcal/mol (**Table 2**). However, it is worth inspecting the ligands closest to the control's binding energy score such as pinobanksin-3-O-butyrate (-9.2±0.1 kcal/mol). As shown in **Figure 3**, two oxygen atoms of this ligand form H-bond interaction with Ala 223 and Leu 171. Another oxygen atom exhibit carbon hydrogen interaction with Ser 170. Both of the aromatic rings form interactions with different amino acid residues. The pi electrons of one of the aromatic rings has interaction with the alkyl group of Ala 223. While in the other aromatic ring, its pi electrons have an interaction with the aromatic side chain of Tyr 177, alkyl group of Leu 126 and forms a pi-sigma interaction with Val 180.

Aldose reductase catalyzes the conversion of glucose into sorbitol with NADPH as a cofactor. In a hyperglycemic system, the exhaustion of NADPH can affect other important biochemical pathways while the accumulation of sorbitol

Table 1. Range of binding energy scores of all the docked ligands to various diabetes-related enzymes.

Ligands	Range of binding energy score (kcal/mol)					
	11β-hydroxy-steroid dehydro-genase 1 (4K1L)	**aldose reductase (3G5E)**	**glutamine: fructose-6-phosphate amidotrans-ferase (2ZJ4)**	**Glucokinase (1V4S)**	**N-terminal maltase gluco-amylase (2QMJ)**	**human pancrea-tic α-amylase (3BAJ)**
Apigenin	-8.0 to -8.8	-7.4 to -9.7	-6.9 to -7.5	-5.9 to -8.6	-6.4 to -7.5	-7.3 to -9.3
Artepillin C	-7.3 to -9.1	-8.6 to -9.3	-6.3 to -7.2	-6.2 to -7.6	-6.7 to -7.6	-6.6 to -7.4
Luteolin-5-methyl ether	-8.4 to -9.0	-7.7 to -9.7	-6.5 to -7.8	-6.3 to -7.4	-6.5 to -7.5	-7.6 to -9.6
Pinobanksin-3-O-butyrate	-8.1 to -9.2	-7.2 to -9.4	-6.0 to -7.8	-5.7 to -7.2	-5.6 to -7.1	-6.5 to -8.0
Pinobanksin-5,7-dimethyl ether	-7.8 to -9.0	-6.8 to -9.2	-6.1 to -7.7	-6.0 to -7.5	-5.8 to -6.8	-6.8 to -8.4
Pinocembrin-5-methyl ether	-7.8 to -8.7	-7.1 to -9.4	-6.2 to -7.6	-6.1 to -7.6	-6.0 to -7.3	-7.5 to -8.7
Control	-5.4 to -9.3[1]	-7.9 to -9.8[2]	-6.3 to 6.6[3]	-5.3 to -7.1[4]	-6.7 to -7.2[5]	-7.1 to -7.9[5]

Note: [1]Carbenoxolone; [2]Epalrestat; [3]Fructose 6-phosphate; [4]RO0281675; [5]Acarbose

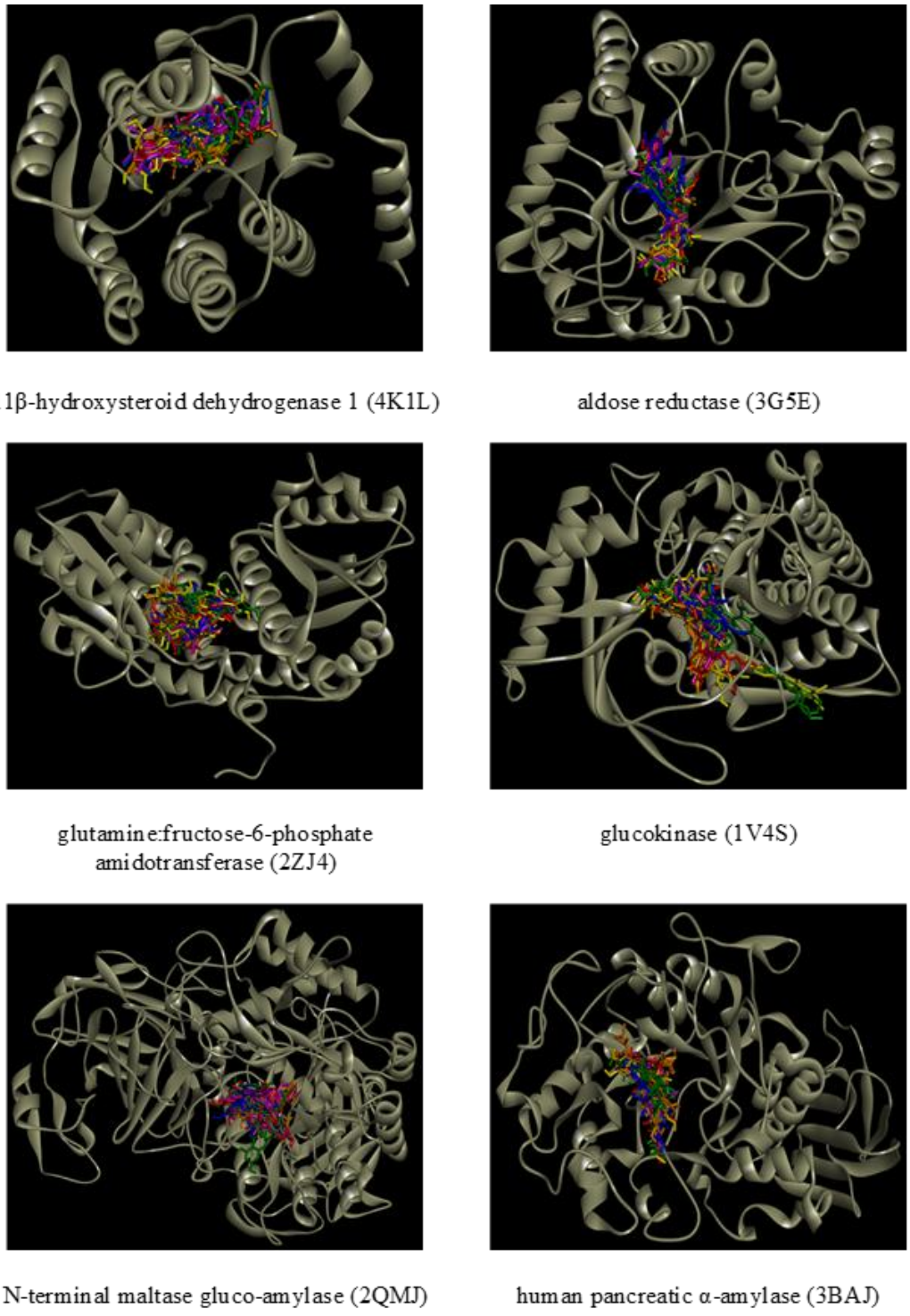


Figure 2. Location of all the docked ligands to the various diabetes-related enzymes (red: apigenin; orange: artepillin C; yellow: luteolin-5-methyl ether; green: pinobanksin-3-O-butyrate, blue: pinobanksin-5,7-dimethyl ether; violet: pinocembrin-5-methyl ether).

Table 2. Binding energy score of the ligands to various diabetes-related enzymes.

Ligands	Average binding energy score (kcal/mol)*					
	11β-hydroxysteroid dehydrogenase 1 (4K1L)	**aldose reductase (3G5E)**	**glutamine:fructose-6-phosphate amidotransferase (2ZJ4)**	**glucokinase (1V4S)**	**N-terminal maltase gluco-amylase (2QMJ)**	**human pancreatic α-amylase (3BAJ)**
Apigenin	-8.8±0.0	-9.7±0.0	-7.5±0.0	-8.6±0.1	-7.5±0.0	-9.3±0.0
Artepillin C	-9.1±0.0	-9.3±0.0	-7.2±0.2	-7.6±0.1	-7.6±0.0	-7.4±0.1
Luteolin-5-methyl ether	-9.0±0.0	-9.7±0.1	-7.8±0.1	-7.4±0.0	-7.5±0.0	-9.6±0.1
Pinobanksin-3-O-butyrate	-9.2±0.1	-9.4±0.1	-7.8±0.0	-7.2±0.1	-7.1±0.0	-8.0±0.0
Pinobanksin-5,7-dimethyl ether	-9.0±0.0	-9.2±0.1	-7.7±0.1	-7.5±0.0	-6.8±0.0	-8.4±0.0
Pinocembrin-5-methyl ether	-8.7±0.1	-9.4±0.1	-7.60.0	-7.6±0.3	-7.3±0.0	-8.7±0.1
Control	-9.3±0.0[1]	-9.8±0.1[2]	-6.6±0.1[3]	-7.1±0.1[4]	-7.2±0.0[5]	-7.9±0.0[5]

Note: [1]Carbenoxolone; [2]Epalrestat; [3]Fructose 6-phosphate; [4]RO0281675; [5]Acarbose
*Average ± SD

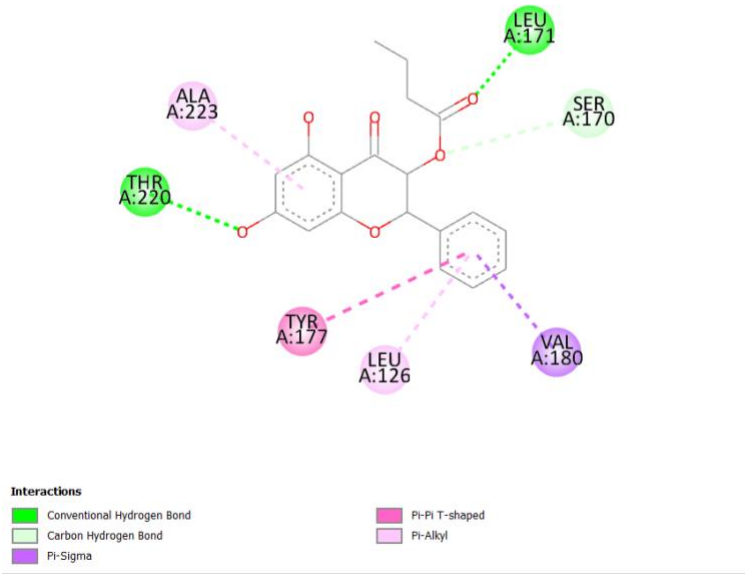


Figure 3. Ligand interaction diagram of pinobanksin-3-O-butyrate with 11β-hydroxysteroid dehydrogenase type 1.

and fructose (the end-product of the polyol pathway) can degrade cellular performance in the body (Dunlop, 2000; Kawanishi et al., 2003). Epalrestat was used as the control for the docking with aldose reductase. It is a carboxylic acid-based drug commonly used to treat retinopathy and neuropathy (Grewal et al., 2016). None of the compounds in stingless bee propolis docked in aldose reductase were predicted to have a more negative binding energy score than that of epalrestat (-9.8±0.1 kcal/mol). The binding energy score of apigenin and luteolin-5-methyl ether is the closest to that of the control which is -9.7±0.0 kcal/mol and -9.7±0.1 kcal/mol, respectively (**Table 2**). One oxygen atom of apigenin form H-bond interaction with Trp 111. The pi electrons of apigenin interact with the thiol group of Cys 80, alkyl group of Leu 300, and indole side chain of Trp 111. Moreover, its pi electrons also form a pi-hydrogen bond interaction with the thiol group of Cys 303 and a pi-pi T-shaped interaction with the phenyl side chain of Phe 122 (**Figure 4A**). On the other hand, luteolin-5-methyl ether forms an H-bond and a pi-sulfur interaction with Cys 80. Its pi electrons also interact with the aromatic rings of Trp 20, Trp 111 and Phe 122 as well as with the alkyl group of Trp 111 and Leu 300, and with the thiol group of Cys 303 (**Figure 4B**).

Interest has also raised recently on the inhibition of glutamine:fructose-6-phosphate amidotransferase (GFAT) as a form of supplementary diabetes treatment. This protein is the first and the rate-limiting enzyme in the hexosamine biosynthesis pathway, whose high flux may be linked to a rise in

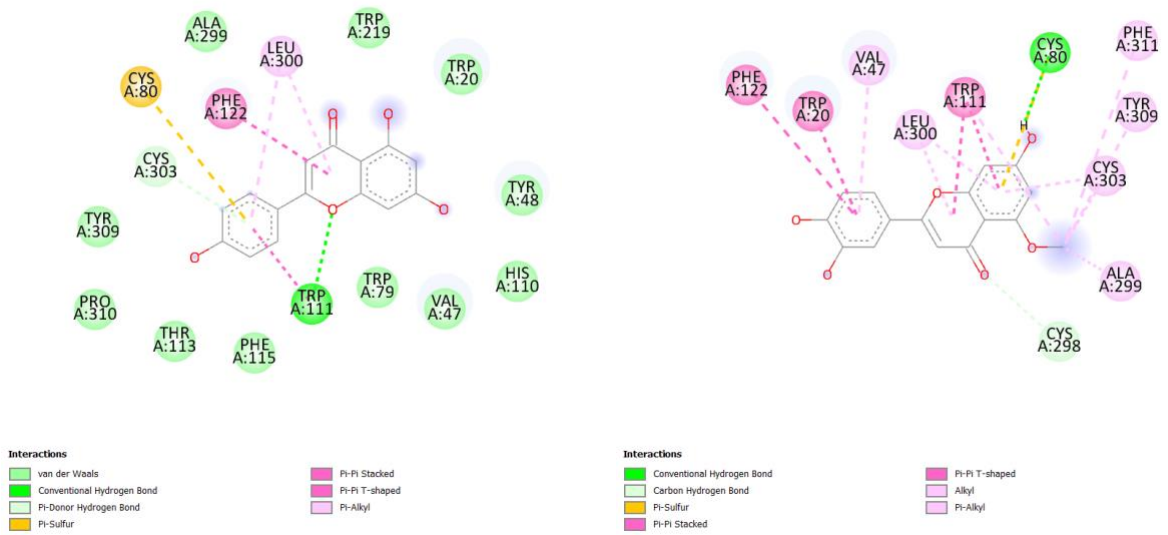


Figure 4. Ligand interaction diagram of (A) apigenin and (B) luteolin-5-methyl ether with aldose reductase.

insulin resistance (Buse, 2006). No pharmaceutical GFAT inhibitors have been developed yet as such the control utilized in this study was the enzyme's substrate, fructose 6-phosphate. It can be observed that all of the propolis ligands' binding energy score exceed that of the control (-6.6±0.1 kcal/mol), with luteolin-5-methyl ether and pinobanksin-3-O-butyrate having the most negative binding energy score of -7.8±0.1 kcal/mol and -7.8±0.0 kcal/mol, respectively (**Table 2**). The good binding of luteolin-5-methyl ether is due to the three H-bond interaction with Thr 375, Ser 376 and Ser 422. Its pi electrons also interact with Leu 673 and Val 677 (**Figure 5A**). On the other hand, the good binding of pinobanksin-3-O-butyrate is due to the two H-bond interaction with Val 471 and Lys 675. Its pi electrons also interact with the alkyl group of Val 677 and Cys 373. Moreover, this ligand also interacts with various amino acid residues via Van der Waals interaction (**Figure 5B**).

The activation of glucokinase has also been a target for controlling blood glucose levels in hyperglycemic patients. This enzyme catalyzes the phosphorylation of glucose into glucose-6-phosphate, this in turn leads to the promotion of insulin secretion and glycogen production (Li et al., 2020). Studies have shown that the enzyme contains an active site (with which glucose binds to) and an allosteric site, which has been the target of most drugs. By binding with glucokinase in this allosteric site, its affinity to catalyze glucose phosphorylation in its active site is increased (Coghlan & Leighton, 2008). The control used for this enzyme is RO0281675, a glucokinase activator currently under development (Haynes et al., 2010). All of the propolis ligands had a more negative binding energy score compared to that of the control which is -7.1±0.1 kcal/mol. Among these ligands, apigenin had the best binding energy score which is -8.6±0.1 kcal/mol (**Table 2**).

The strong binding of this ligand is due to various interactions such as two H-bonding with Tyr 215. Its pi electrons also interact with the alkyl group of Pro 66, Val 62, Ile 211, Val 452, Val 455 and Ala 456. Moreover, it also exhibits a pi-pi T-shaped interaction with the aromatic side chain of Tyr 214. The pi electrons of Tyr 214 also interact with the hydroxyl group of apigenin (**Figure 6**).

Maltase glucoamylase (MGAM) is an alpha-glucosidase in the brush border of the small intestine, together with sucrase isomaltase. Both enzymes catalyze the final steps of carbohydrate digestion in the intestine. Thus, their inhibition aids in decreasing blood glucose levels in the body (Sim et al., 2010). The control used for MGAM docking was acarbose, a pseudotetrasaccharide that competes against oligosaccharides thus preventing its cleavage into monosaccharides. Among the propolis ligands, artepillin C had the most negative binding energy score which is -7.6±0.0 kcal/mol compared to that of the control (-7.2±0.0 kcal/mol; **Table 2**). This ligand forms four H-bond interaction with Asp 203, Asp 542 and Gln 603. The pi electrons of the aromatic ring also interact with the aromatic ring of Trp 406 and anion side chain of Asp 542. Moreover, some of the ligands alkyl groups also interact with Tyr 299, Ile 328, Ile 364, Trp 406 and Phe 450 (**Figure 7**)

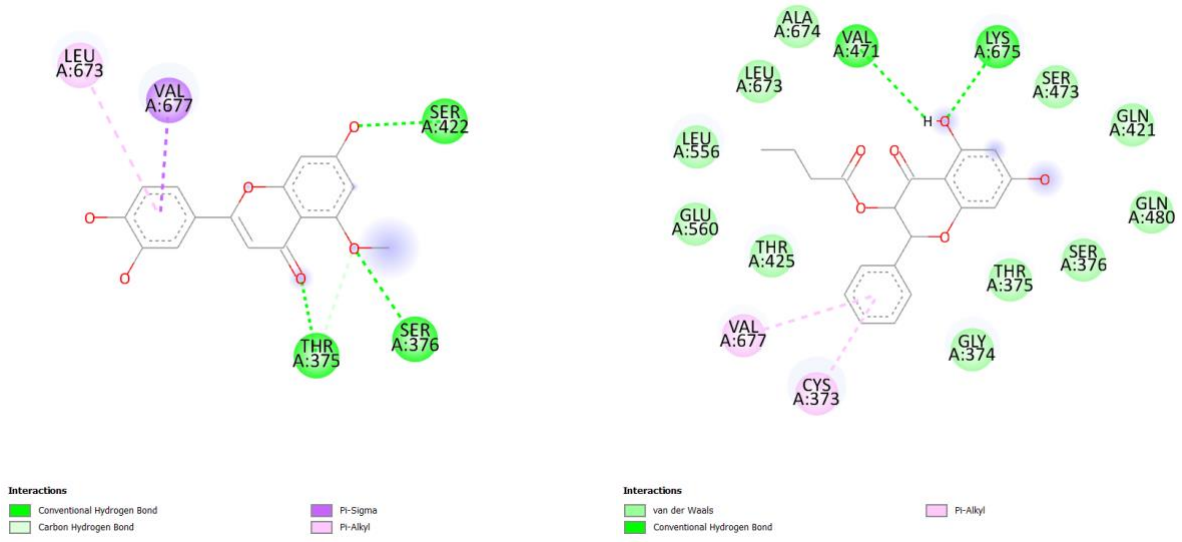


Figure 5. Ligand interaction diagram of (A) luteolin-5-methyl ether and (B) pinobanksin-3-O-butyrate with glutamine:fructose-6-phosphate amidotransferase.

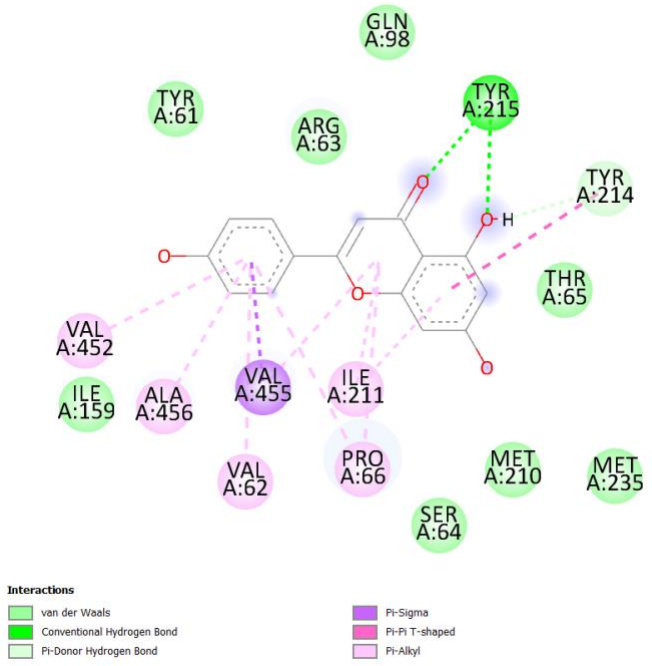


Figure 6. Ligand interaction diagram of apigenin with glucokinase.

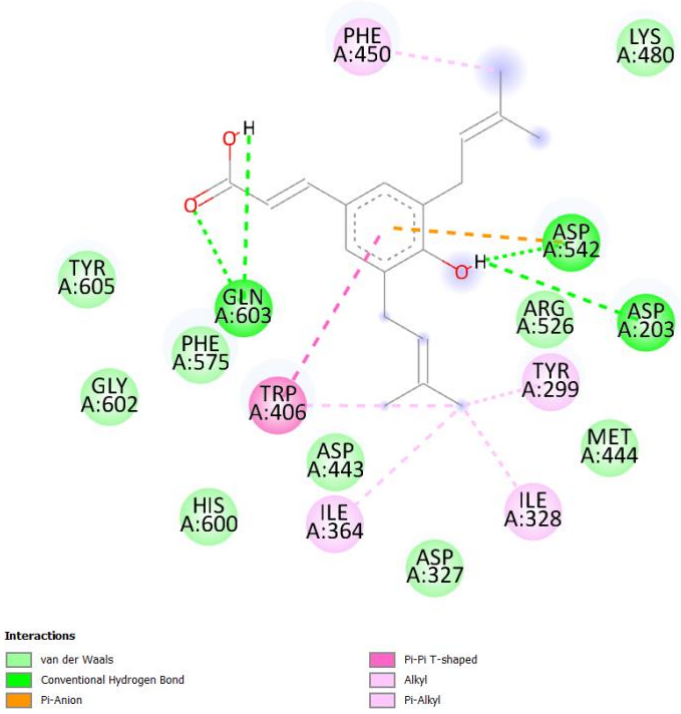


Figure 7. Ligand interaction diagram of artepillin C with N-terminal maltase glucoamylase.

Human pancreatic α-amylase (HPA) is one of two amylases in the body, the other being salivary α-amylase. These two enzymes catalyze the hydrolysis of starch into oligosaccharides that are further degraded into glucose (Dandekar et al., 2021). Its inhibition aids in decreasing blood glucose levels in the body. Acarbose was also used as control in docking with HPA. All of the propolis compounds except for artepillin C resulted to a more negative binding energy score compared to that of the control (-7.9±0.0 kcal/mol). Luteolin-5-methyl ether had the most negative binding energy score which is -9.6±0.1 kcal/mol (**Table 2**). The strong binding of this ligand is due to two H-bond interaction with Gln 63 and Asp 197. Moreover, its pi electrons also interact with the aromatic side chain of Trp 59 and Tyr 62. There is also an unfavorable donor-donor interaction between one of the hydroxyl group of luteolin-5-methyl ether and His 299 (**Figure 8**).

The Lipinski's rule-of-five (Ro5) is used to assess the drug-likeness of chemical compounds and potential medicines. The ligands that comply with Lipinski's Ro5 or having no more than one violation is considered to have the potential to become a drug (Sailah et al., 2021; Yang et al., 2020). **Table 3** shows the predicted ADMET properties of the propolis compounds based on Swiss ADME. All of the compounds are found to be soluble in water and exhibit good gastrointestinal absorption. However, only two of the propolis compounds do not penetrate the blood brain barrier (BBB). Since the target of this study are diabetes-related enzymes, it is preferential that these compounds are not BBB permeant since it can have secondary effects once it is in the brain. Based on the results, all of the propolis compounds inhibited one or more of the cytochrome P450 enzymes particularly CYP1A2, CYP2C19, CYP2C9, CYP2D6, and/or CYP3A4. Cytochrome P450 is an important detoxifying enzyme that works by oxidizing foreign organic compounds and facilitate its excretion (Foroozesh et al., 2019). Thus, it would be best if compounds do not inhibit CYP450 enzymes because these enzymes are responsible for drug metabolism. Even though these compounds inhibit CYP450 enzymes, all of the propolis compounds show similar properties to drugs (drug-likeness) as they do not violate Lipinski's Ro5 and all have a bioavailability of 0.55 or higher. Moreover, with the exception of artepillin C, all of the other compounds comply with lead-likeness. Lead-likeness is the structural and physicochemical similarity of a potential drug to a reference (lead) compound for further drug development (Polinsky, 2008). These results suggest that these compounds may exhibit similarities to an orally active drug and can be used for drug development. In terms of the ADMET properties, pinobanksin-3-O-butyrate showed the highest potential for drug development.

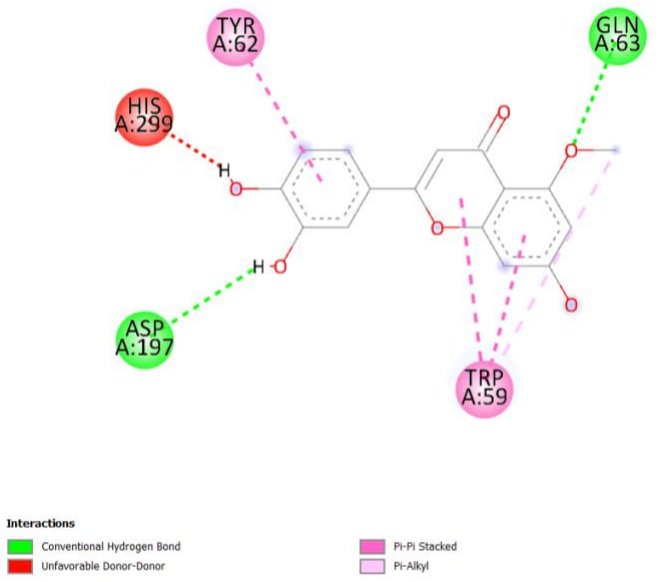


Figure 8. Ligand interaction diagram of luteolin-5-methyl ether with human pancreatic α-amylase.

Table 3. Predicted ADMET properties based on SWISS ADME.

ADMET properties	Ligands					
	Apigenin	**Artepillin C**	**Luteolin-5-methyl ether**	**Pinobanksin-3-O-butyrate**	**Pinobanksin-5,7-dimethyl ether**	**Pinocembrin-5-methyl ether**
Water solubility	Soluble	Moderately soluble	Soluble	Soluble	Soluble	Soluble
GI absorption	High	High	High	High	High	High
BBB permeant	No	Yes	No	No	Yes	Yes
CYP inhibitor	CYP1A2, CYP2D6, CYP3A4 inhibitor	CYP2C19, CYP2C9 inhibitor	CYP1A2, CYP2D6, CYP3A4 inhibitor	CYP2C9 inhibitor	CYP2C19, CYP3A4 inhibitor	CYP1A2, CYP2C19, CYP3A4 inhibitor
Bioavailability score	0.55	0.85	0.55	0.55	0.55	0.55
Lipinski (drug-likeness)	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
Lead-likeness	Yes	No; 1 violation: XLOGP3>3.5	Yes	Yes	Yes	Yes

SUMMARY AND CONCLUSION

The potential anti-diabetic properties of compounds present in stingless bee propolis (apigenin, artepillin C, luteolin-5-methyl ether, pinobanksin-3-O-butyrate, pinobanksin-5,7-dimethyl ether, and pinocembrin-5-methyl ether) were screened through molecular docking with diabetes-relevant enzymes. Results showed that all ligands have good binding affinities to pre-defined binding sites. Thus, these compounds can be a potential anti-diabetic drug. Among the ligands used, pinobanksin-3-O-butyrate showed the highest potential for drug development due to its predicted high GI absorption, good water solubility and bioavailability score, non-BBB permeant, and does not violate Lipinski's Ro5.

It is recommended to use other software for molecular docking as this could determine whether or not the software used in this study affected the results. Moreover, molecular dynamics may be performed to further validate the docking results.

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