COMPUTATIONAL PREDICTION OF SIDE EFFECTS OF ORAL ANTIDIABETIC DRUGS ON KIDNEY ENZYMATICS

PANDANWANGI, S. T. W.[1*] – SUBAGJA[1] – ZUNIARTO, A. A.[1] – AISYAH, S. T. W.[1]

[1] *Faculty of Pharmacy, Yayasan Pendidikan Imam Bonjol Majalengka University, West Java, Indonesia.*

**Corresponding author*
e-mail: sitipandanwangitw[at]gmail.com

(Received 07th November 2025; revised 23rd February 2026; accepted 08th March 2026)

Abstract. Diabetes mellitus is a metabolic disorder that causes hyperglycemia and requires long-term treatment that carries the risk of side effects, including decreased kidney function. The study aims to determine the affinity and binding values between oral antidiabetic drugs and target proteins, as well as to computationally predict the toxicity and side effects of these drugs on renal enzymes using molecular docking and the Toxtree application. This study employs the molecular docking method to predict interactions and affinities between test compounds of oral antidiabetic drugs and target proteins. The affinity values of oral antidiabetic drugs toward ACE were as follows: Glimepiride -2.2 kcal/mol, Repaglinide 2.9 kcal/mol, Metformin -2.3 kcal/mol, Pioglitazone -2.0 kcal/mol, Acarbose 16.3 kcal/mol, Sitagliptin -1.9 kcal/mol, Dapagliflozin 0 kcal/mol, for the VDR protein: Glimepiride -11.2 kcal/mol, Repaglinide -8.1 kcal/mol, Metformin -5.1 kcal/mol, Pioglitazone -9.8 kcal/mol, Acarbose -7.6 kcal/mol, Sitagliptin -10.3 kcal/mol, Dapagliflozin -9.4 kcal/mol, on the EPOR protein: Glimepiride 16.0 kcal/mol, Repaglinide 0 kcal/mol, Metformin -3.3 kcal/mol, Pioglitazone -1.4 kcal/mol, Acarbose 14.2 kcal/mol, Sitagliptin -0.2 kcal/mol, Dapagliflozin -0.2 kcal/mol, on the COX-2 protein, namely Glimepiride -11.0 kcal/mol, Repaglinide -8.1 kcal/mol, Metformin -5.6 kcal/mol, Pioglitazone -9.1 kcal/mol, Acarbose -7.7 kcal/mol, Sitagliptin -9.7 kcal/mol, Dapagliflozin -8.5 kcal/mol. Based on computational analysis, Glimepiride and Sitagliptin exhibit the strongest and most stabel interactions, particularly with the VDR and COX-2 proteins, while Metformin and Dapagliflozin have lower affinities. Drug interactions with target proteins are dominated by hydrogen bonds, hydrophobic, and electrostatic interactions. It is predicted that oral antidiabetic drugs with side effects are Glimepiride and Sitagliptin.
Keywords: *oral antidiabetics, side effects, molecular docking, binding affinity*

Introduction

The 10th edition of the International Diabetes Federation confirms that diabetes is one of the fastest-growing global health problems of the 21st century. In 2021, approximately 537 million people had diabetes, and this number is expected to reach 643 million by 2030 and 783 million by 2045. In general, diabetes is classified into several clinical forms, such as type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, as well as other types caused by specific factors, including genetic disorders, disorders of the exocrine pancreas, or due to the use of certain drugs. Patients with diabetes mellitus require lifelong therapy to relieve symptoms, slow disease progression, and prevent complications. However, long-term use of antidiabetic drugs carries the risk of certain side effects. Side effects arising from a treatment can affect the patient's quality of life, both physically and economically. In Indonesia, the incidence of drug side effects varies between 0.9% and 99%, depending on the type of drug used, the duration of treatment, and the dose given in therapy. Adverse drug reactions are unintended reactions that occur when a drug is used at therapeutic doses during clinical practice. These events can negatively impact a patient's quality of life and potentially cause morbidity and even mortality.

Management of type 2 diabetes continues to evolve as clinical research enhances understanding of drug effects on physiological systems and patient outcomes. For instance, newer studies have shown specific antihyperglycemic agents such as sitagliptin can influence hematological and renal parameters in patients with type 2 diabetes (Alnaser et al., 2025). Additionally, metformin's role in cardiovascular regulation in diabetic patients is complex, with some trials indicating adverse effects on orthostatic blood pressure recovery (Hansen et al., 2020). In contrast, other research suggests metformin may also be associated with reduced mortality in COVID-19 patients with pre-existing diabetes (Luo et al., 2020), underscoring its multifaceted impact. The prevalence of adverse drug reactions among diabetic populations has been systematically reviewed in Indonesia, revealing significant patterns that warrant clinical attention (Maharani and Yugatama, 2023). Furthermore, agents like vitamin D have been implicated in metabolic regulation and potentially prevention strategies for hyperglycemia (Monapati et al., 2023). Work on diabetic nephropathy demonstrates ongoing progress in understanding prognosis and treatment targets, data that are critical for guideline development (Selby and Taal, 2020). Interventions targeting fluid balance and renal protective mechanisms, such as SGLT-2 inhibitors like dapagliflozin, continue to garner clinical interest (Oka et al., 2023). Finally, global studies on drug safety monitoring provide methodological insight into pharmacovigilance and can inform diabetes management frameworks (Suku et al., 2015).

Long-term use of oral antidiabetic medications can affect kidney function, leading to diabetic nephropathy. Diabetic nephropathy is a clinical syndrome in patients with diabetes mellitus characterized by uremia and microalbuminuria. This condition can be triggered by medication side effects, errors in selecting an oral antidiabetic, and inappropriate dosing. Diabetic nephropathy is a significant health challenge. It affects up to 50% of individuals with diabetes and is a leading cause of advanced kidney failure, which typically requires dialysis or a kidney transplant. Computational research is research that uses computational technology or in silico, Toxtree is one of the software for in silico research, Toxtree is used to predict test compounds (ligands) to identify potential side effects or toxic properties that may be caused by the compound, aiming to determine the potential toxicity of the compound. Molecular docking is a computer-based simulation method used to predict the interaction between a ligand (a small compound) and a receptor or protein, by placing the ligand in the active site of the receptor. The results of molecular docking of the test ligand to its receptor can be expressed in terms of binding energy and inhibition constant values. Prediction is the systematic activity of estimating events that are likely to occur in the future by utilizing historical data and current conditions to minimize the error rate. The goal of prediction is not to provide completely accurate results, but rather to approximate the likely reality. Predictions serve as a picture of possible future situations and serve as an important basis for planning and decision-making.

Materials and Methods

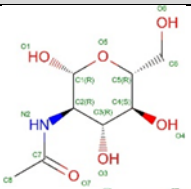
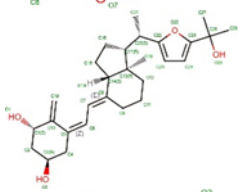
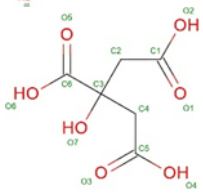
This research was conducted using the Molecular docking method, which is a technique used to predict the interaction between compounds (ligands) and target proteins, by assessing their conformation and binding affinity. The independent variable is an oral antidiabetic drug compound. The oral antidiabetic drugs used are Glimepiride, Repaglinide, Metformin, Pioglitazone, Acarbos, Sitagliptin, and Dapaglifozin. The

dependent variable in this study is the prediction of drug side effects on the kidneys (binding affinity value, binding type, Toxtree parameter, Benigni/Rulebase Crammer Rules, Croes TCC Decision Tree, and Verhaar Scheme).

Results and Discussion

The following are the characteristics of the target proteins used for the study (*Table 1*, *Table 2* and *Table 3*). Glimepiride is one of the most widely used antidiabetic drugs in the sulfonylurea class in Indonesia. Glimepiride is a second-generation sulfonylurea with a mechanism of action that activates pancreatic β-cells. After Glimepiride binds to specific sulfonylurea receptors, it closes ATP-sensitive potassium channels, resulting in insulin release from pancreatic β-cells. Based on the results of glimepiride docking to the target protein, Glimepiride occupies the ACE protein with an affinity of -2.2. This affinity is almost similar to the natural ligand of the ACE protein, which is -3.5, and also almost similar to Captopril as a positive control for the ACE protein, which is -2.7. This allows Glimepiride to work like captopril against the ACE protein. It is possible that glimepiride can also have activity against blood pressure. Glimepiride binds to the VDR protein with an affinity of -11.2, while the affinity of its natural ligand is -13.7 and the affinity of the positive control on the VDR protein is -12.2. This allows glimepiride to work similarly to Vitamin D3 on the VDR protein. The role of vitamin D in diabetes is that it can play a role in insulin resistance, thereby reducing glycemic values. Vitamin D acts directly on beta cells by facilitating insulin secretion from the binding of 1,25(OH)2D3 to the VDR in the nucleus and indirectly by regulating calcium flow in these cells (Monapati et al., 2023). Previous studies have shown that vitamin D supplementation alone increases insulin levels and has an additive effect on the action of glimepiride. Glucose reductions were significantly greater when glimepiride and vitamin D were administered as a combination therapy.

Table 1. *Affinity and RMSD values of natural ligands.*

Target proteins	Affinity and RMSD values of natural ligands	Affinity value	RMSD
Angiotensin Converting Enzym (ACE)		-3,5	0.0
Vitamin D Receptor (VDR)		-13,7	0.0
Erythropoietin Receptor (EPOR)		-4,2	0.0

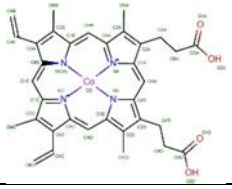
Cyclooxygenase -2 (COX-2)		-11,4	0.0

***Table 2**. Affinity value of control to target protein.*

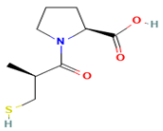
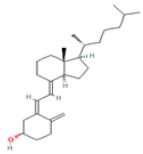
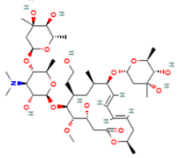
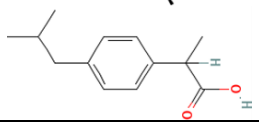
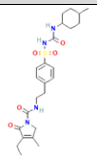
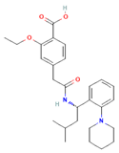
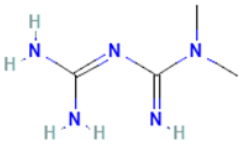
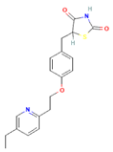
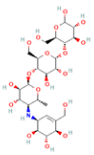
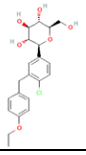
Compound	Compound structural	Target Proteins	Affinity value	RMSD
Captopril		ACE	-2,7	0.0
Vitamin D3		VDR	-12,2	0.0
Epoetin alfa		EPOR	0	0.0
Ibuprofen		COX-2	-7,1	0.0

***Table 3**. Affinity Value of Oral Antidibetic with Target Proteins ACE, VDR, EPOR, and COX-2.*

Compound	Compound structural	Target Proteins	Affinity value	RMSD
Glimepirid		ACE VDR EPOR COX-2	-2,2 -11,2 16,0 -11,0	0.0 0.0 0.0 0.0
Repaglinid		ACE VDR EPOR COX-2	2,9 -8,1 0 -8,1	0.0 0.0 0.0 0.0
Metformin		ACE VDR EPOR COX-2	-2,3 -5,1 -3,3 -5,6	0.0 0.0 0.0 0.0
Pioglitazon		ACE VDR EPOR COX-2	-2,0 -9,8 -1,4 -9,1	0.0 0.0 0.0 0.0
Acarbose		ACE VDR EPOR COX-2	16,3 -7,6 14,2 -7,7	0.0 0.0 0.0 0.0
Pioglitazon		ACE	-1,9	0.0

Dapaglifozin		VDR	-10,3	0.0
		EPOR	-0,2	0.0
		COX-2	-9,7	0.0
		ACE	0	0.0
		VDR	-9,4	0.0
		EPOR	-0,2	0.0
		COX-2	-8,5	0.0

Glimepiride binds to the EPOR protein with an affinity of 16.0, which is very low, suggesting it may not bind to the EPOR protein. Glimepiride binds to COX-2 with an affinity of -11.0, similar to the natural ligand COX-2 protein, which is -13.7, but differs from its positive control, ibuprofen, which has an affinity of -7.1. The different affinity values are possible due to their opposing properties. Ibuprofen acts as a COX-2 inhibitor by inhibiting the activity of the COX-2 enzyme, which plays a role in the production of prostaglandins, compounds involved in pain and inflammation. One type of prostaglandin, prostacyclin (PGI2), plays a crucial role in maintaining normal kidney function. Therefore, inhibiting prostacyclin formation can trigger fluid retention in the body. Therefore, it's possible that glimepiride may have a beneficial effect, improving fluid retention due to its opposite effect to ibuprofen. However, this requires further investigation, as no previous studies have shown that glimepiride can improve fluid retention.

Repaglind binds to the VDR protein with an affinity of -8.1, compared to the affinity of its natural ligand of -13.7 and the affinity of the positive control of the VDR protein of -12.2. These different affinity values allow repaglinide to inhibit the VDR protein due to its opposite effect on the VDR protein compared to vitamin D3. Vitamin D3 is a protective factor in the development of insulin resistance. This is likely because vitamin D3 effectively inhibits inflammation, which is a major factor in inducing insulin resistance. Vitamin D3 deficiency can lead to reduced insulin secretion. Studies have now established a linear relationship between vitamin D3 and insulin resistance. Therefore, within a certain range, maintaining higher vitamin D3 levels is crucial for preventing insulin resistance, and these findings provide guidance for clinical practice. So Repaglinide should be given together with vitamin D3 to increase the therapeutic effect. Repaglinide binds to the EPOR protein with an affinity of 0. Its affinity is very low, meaning it may not bind to the EPOR protein. Repaglinide binds to the COX-2 protein with an affinity of -8.1, unlike the natural ligand of the COX-2 protein, which is -13.7, but is almost identical to its positive control, ibuprofen, with an affinity of -7.1. Repaglinide's affinity value, which is almost similar to ibuprofen, allows repaglinide to work similarly to ibuprofen on the COX-2 protein. Ibuprofen acts as a COX-2 inhibitor by inhibiting the activity of the COX-2 enzyme, which plays a role in the production of prostaglandins, compounds involved in pain and inflammation responses. One type of prostaglandin, prostacyclin (PGI2), plays an important role in maintaining normal kidney function. Therefore, inhibiting prostacyclin formation can trigger fluid retention in the body.

Metformin is an oral antidiabetic drug from the biguanide group that can be used or given in most cases of type 2 diabetes. Based on the results of metformin docking to the target protein, metformin occupies the ACE protein with an affinity of -2.3. This affinity is almost similar to the natural ligand of the ACE protein, which is -3.5, also almost similar to Captopril as a positive control of the ACE protein, which is -2.7. This allows metformin to work like captopril against the ACE protein. It is possible that metformin

can also have blood pressure lowering activity. According to previous studies, metformin treatment combined with insulin can affect the early orthostatic blood pressure response because metformin treatment reduces orthostatic blood pressure 30 seconds after standing. Metformin causes lactic acidosis. Several risk factors contribute to the development of lactic acidosis, including liver or kidney impairment, advanced age, surgery, hypoxia, and alcoholism. These risk factors can lower blood pH or prevent proper lactate removal. Although lactic acidosis is a rare side effect, it can lead to serious consequences such as hypotension, hypothermia, and even death. Concomitant use of captopril with metformin can potentially increase metformin's activity, which can lead to excessive blood glucose reduction. This is because ACE inhibitors like captopril can potentiate the hypoglycemic effects of oral antidiabetic drugs. Therefore, caution is advised in diabetic patients receiving oral antidiabetic drugs in this class. Concomitant use of captopril is feared to cause excessive hypotension.

Metformin binds to the VDR protein with an affinity of -5.1, compared to the affinity of its natural ligand of -13.7 and the affinity of the positive control for the VDR protein of -12.2. These different affinity values allow metformin to inhibit the VDR protein due to its antagonistic effect on the VDR protein by the drug Vitamin D3. Vitamin D deficiency is associated with decreased insulin secretion and increased insulin resistance. According to previous research, users of oral antidiabetic drugs were observed in a cohort study to have a mean serum 25(OH)D concentration of 7.3 nmol/L lower than those of diabetics not taking these drugs. One group has suggested that an intrinsic limitation of this study is that any potential effect of metformin on lowering vitamin D levels may have been confounded as a result of supplement use when the deficiency was diagnosed. Metformin binds to the EPOR protein with an affinity of -3.3, almost identical to the affinity of its natural ligand, which is -4.2. This means that the affinity of metformin is relatively low. According to previous research, long-term use of metformin can cause anemia associated with vitamin B12 deficiency. This conclusion was obtained based on the patient's history of metformin use, clinical examination results, and laboratory data analysis that showed hematological disorders, low serum vitamin B12 levels, increased total homocysteine levels, and methylmalonic acid levels. In addition, a study conducted by Thambiah stated that approximately 10–30% of patients experience anemia due to metformin, which is known to inhibit vitamin B12 absorption. Metformin binds to the COX-2 protein with an affinity of -5.6, unlike the natural ligand of the COX-2 protein, which is -13.7, but is almost identical to its positive control, ibuprofen, with an affinity of -7.1. Metformin's affinity value, which is almost similar to ibuprofen, allows it to work similarly to ibuprofen on the COX-2 protein. Ibuprofen acts as a COX-2 inhibitor by inhibiting the activity of the COX-2 enzyme, which plays a role in the production of prostaglandins, compounds involved in pain and inflammation responses. One type of prostaglandin, prostacyclin (PGI2), has an important function in maintaining normal kidney function. Therefore, inhibiting prostacyclin formation can trigger fluid retention in the body.

Pioglitazone is a drug used in the treatment of type 2 diabetes mellitus. Pioglitazone is the third marketed oral antidiabetic drug from the thiazolidinedione group. The mechanism of thiazolidinediones is to increase insulin sensitivity by acting on muscle, adipose, and liver tissues. Thiazolidinediones increase glucose utilization in peripheral tissues and, to some extent, reduce glucose production in the liver. This action involves the activation of the nuclear receptor, the gamma isoform of the peroxisome proliferator-activated receptor (PPAR-gamma). Based on the results of pioglitazone

docking with the target protein, pioglitazone occupies the ACE protein with an affinity of -2.0. This affinity is almost the same as the natural ligand of the ACE protein, which is -3.5, and also almost similar to Captopril as a positive control for the ACE protein, which is -2.7. This allows pioglitazone to work like captopril on the ACE protein. It is possible that pioglitazone can also have blood pressure-lowering activity. According to clinical data clearly shows that thiazolidinediones have blood pressure lowering effect in hypertensive, diabetic and non-diabetic patients. Pioglitazone binds to the VDR protein with an affinity of -9.8, compared to its natural ligand affinity of -13.7, and closer to the positive control affinity of -12.2. This affinity value, which is closer to the positive control, allows pioglitazone to act similarly to vitamin D3 on the VDR protein. Vitamin D stimulates insulin secretion by pancreatic β cells; thus, vitamin D deficiency is associated with insulin resistance. Previous research has shown that pioglitazone can reduce insulin resistance but can increase fluid retention, making it contraindicated in patients with heart failure.

Pioglitazone binds to the EPOR protein with an affinity of -1.4, slightly different from the affinity of its natural ligand, which is -4.2. This indicates low affinity for pioglitazone, according to previous studies. Treatment with pioglitazone has been associated with decreased hemoglobin and increased risk of anemia. Thiazolidinediones increase sodium and water retention and thus increase plasma volume, suggesting a basic component of dilution. On the other hand, pioglitazone treatment increases the effectiveness of EPO at lower doses over the long term in patients undergoing hemodialysis, an effect that may be mediated through its insulin-sensitizing effect (Antoniadou et al., 2025). Pioglitazone binds to the COX-2 protein with an affinity of -9.1, unlike the natural ligand of the COX-2 protein, which is -13.7, but is almost identical to its positive control, ibuprofen, with an affinity of -7.1. Pioglitazone's affinity value, which is almost similar to ibuprofen, allows pioglitazone to work similarly to ibuprofen on the COX-2 protein. Ibuprofen acts as a COX-2 inhibitor by inhibiting the activity of the COX-2 enzyme, which plays a role in the production of prostaglandins, compounds involved in pain and inflammation responses. One type of prostaglandin, prostacyclin (PGI2), has an important function in maintaining normal kidney function. Therefore, inhibiting prostacyclin formation can trigger fluid retention in the body. Fluid retention and peripheral edema have been reported in 4–7% of patients treated with pioglitazone, which is 3–4 times more common than placebo, the effect being even greater when combined with other oral antihyperglycemic treatments (up to 15–18%) - and especially insulin therapy (~22%).

Acarbos binds to the ACE protein with an affinity of 16.3, which is very low, suggesting it may not bind to the AC protein. Acarbos binds to the VDR protein with an affinity of -7.6, compared to the affinity of its natural ligand, which is -13.7, and the affinity of the positive control on the VDR protein, which is -12.2. These different affinity values allow acarbos to inhibit the VDR protein due to its opposite effect on the VDR protein from Vitamin D3. Vitamin D3 is a protective factor in the occurrence of insulin resistance. This may be because vitamin D3 can effectively inhibit inflammation, and inflammation is a major factor that induces insulin resistance. Vitamin D3 deficiency can cause reduced insulin secretion. Currently, research has found a linear relationship between vitamin D3 and insulin resistance. Therefore, within a certain range, maintaining higher vitamin D3 levels is crucial for preventing insulin resistance, and these results provide guidance for clinical practice. However, this needs to be studied further because there has been no previous research stating that acarbos

can cause vitamin D3 deficiency which will cause insulin resistance. Acarbos binds to the EPOR protein with an affinity of 14.2, which is very low, so it is possible that acarbos does not bind to the EPOR protein. Acarbos binds to the COX-2 protein with an affinity of -7.7, which is different from the natural ligand of the COX-2 protein, which is -13.7, but almost similar to its positive control, ibuprofen, with an affinity of -7.1. The affinity value of acarbos, which is almost similar to ibuprofen, allows acarbos to work similarly to ibuprofen on the COX-2 protein. Ibuprofen acts as a COX-2 inhibitor by inhibiting the activity of the COX-2 enzyme, which plays a role in the production of prostaglandins, compounds involved in pain and inflammation responses. One type of prostaglandin, prostacyclin (PGI2), has an important function in maintaining normal kidney function. Therefore, inhibiting the formation of prostacyclin can trigger fluid retention in the body.

Based on the results of sitagliptin docking to the target protein, sitagliptin occupies the ACE protein with an affinity of -1.9. This affinity is almost similar to the natural ligand of the ACE protein, which is -3.5, also almost similar to Captopril as a positive control of the ACE protein, which is -2.7. This allows sitagliptin to work like captopril against the ACE protein. It is possible that sitagliptin can also have blood pressure lowering activity. According to previous research that conducted a prospective, multicenter observational study of 205 patients with type 2 diabetes at high risk of cardiovascular disease treated with sitagliptin for 12 months. Sitagliptin also showed a blood pressure lowering effect during the 12-month study period (Nakamura et al., 2016). It is expected to be careful for diabetic patients who receive oral antidiabetic drug therapy in this class if used concomitantly with captopril is feared to cause excessive hypotension Sitagliptin occupies the VDR protein with an affinity of -10.3, whereas the affinity of its natural ligand is -13.7, and the affinity of the positive control for the VDR protein is -12.2. This allows sitagliptin to work similarly to Vitamin D3 on the VDR protein. Several studies have shown that vitamin D plays a crucial role in the functional control of the endocrine pancreas, particularly beta cells. Beta cells contain 1,25(OH)2D3 receptors, but they also include calbindin-D28k, a vitamin D-dependent calcium-binding protein, which is an effector in the vitamin D pathway. Expression of calbindin-D28k has been shown to protect beta cells from cytokine-mediated cell death, thereby reducing the risk of type 2 diabetes. Vitamin D plays a crucial role in overcoming insulin resistance, which results in lower glycemic levels in people with diabetes mellitus. Vitamin D directly affects pancreatic beta cells by stimulating insulin secretion through binding of 1,25(OH)2D3 to the vitamin D receptor (VDR) in the cell nucleus. Indirectly, vitamin D also helps regulate the flow of calcium ions within the cell, which plays a role in the insulin secretion process (Monapati et al., 2023). This allows sitagliptin to work similarly to Vitamin D3 on the VDR protein. Several studies have shown that vitamin D plays a crucial role in the functional control of the endocrine pancreas, particularly beta cells. Beta cells contain 1,25(OH)2D3 receptors, but they also include calbindin-D28k, a vitamin D-dependent calcium-binding protein, which is an effector in the vitamin D pathway. Expression of calbindin-D28k has been shown to protect beta cells from cytokine-mediated cell death, thereby reducing the risk of type 2 diabetes. Vitamin D plays a crucial role in overcoming insulin resistance, which results in lower glycemic levels in people with diabetes mellitus. Vitamin D directly affects pancreatic beta cells by stimulating insulin secretion through binding of 1,25(OH)2D3 to the vitamin D receptor (VDR) in the cell nucleus. Indirectly, vitamin D also helps

regulate the flow of calcium ions within the cell, which plays a role in the insulin secretion process (Alnaser et al., 2025).

Sitagliptin binds to the COX-2 protein with an affinity of -9.7, unlike the natural ligand of the COX-2 protein, which is -13.7, but is almost identical to its positive control, ibuprofen, with an affinity of -7.1. Sitagliptin's affinity value, which is almost similar to ibuprofen, allows sitagliptin to work similarly to ibuprofen on the COX-2 protein. Ibuprofen acts as a COX-2 inhibitor by inhibiting the activity of the COX-2 enzyme, which plays a role in the production of prostaglandins, compounds involved in pain and inflammation responses. One type of prostaglandin, prostacyclin (PGI2), has an important function in maintaining normal kidney function. Therefore, inhibiting prostacyclin formation can trigger fluid retention in the body. Dapagliflozin binds to the ACE protein with an affinity of 0. Its affinity is very low, meaning it may not bind to the ACE protein. Dapagliflozin binds to the VDR protein with an affinity of -9.4, while the affinity of its natural ligand is -13.7 and the affinity of the positive control on the VDR protein is -12.2. This allows dapagliflozin to work in the opposite direction to vitamin D3 on the VDR protein. Several studies have shown that the combination of SGLT2i antidiabetic drugs and vitamin D3 provides synergistic benefits in metabolic improvement and prevention of cardiac autonomic decline, especially in women. The use of this combination therapy resulted in significant improvements in both drowsiness symptoms and quality of life. Dapagliflozin occupies the EPOR protein with an affinity of -0.2, slightly different from the affinity of its natural ligand, which is -4.2. which means that the affinity of dapagliflozin is low, this affinity value is the same as the affinity of sitagliptin to the EPOR protein, but based on previous research, the two are opposites where sitagliptin can reduce EPO but dapagliflozin actually increases EPO. According to previous research, the low dose of dapagliflozin (5 mg) used in the study was found to increase the number of red blood cells, hemoglobin, and hematocrit levels in elderly type 2 diabetes sufferers with kidney disorders. Treatment with dapagliflozin produces clinically significant increases in Hb levels in patients with type 2 diabetes mellitus and results in improvement and prevention of anemia.

Dapagliflozin binds to the COX-2 protein with an affinity of -8.5, which is different from the natural ligand of the COX-2 protein, which is -13.7, but almost similar to its positive control, ibuprofen, with an affinity of -7.1. The affinity value of dapagliflozin, which is almost similar to ibuprofen, allows dapagliflozin to work similarly to ibuprofen on the COX-2 protein. However, this is different from previous studies that stated that dapagliflozin improved fluid retention and maintained euvolemic fluid status in patients with CKD, which shows that SGLT2 inhibitors provide sustained fluid homeostatic action in patients with various fluid backgrounds (Oka et al., 2023).

Conclusion

The affinity values of oral antidiabetic drugs toward ACE were as follows: Glimepiride -2.2 kcal/mol, Repaglinide 2.9 kcal/mol, Metformin -2.3 kcal/mol, Pioglitazone -2.0 kcal/mol, Acarbose 16.3 kcal/mol, Sitagliptin -1.9 kcal/mol, Dapagliflozin 0 kcal/mol, for the VDR protein: Glimepiride -11.2 kcal/mol, Repaglinide -8.1 kcal/mol, Metformin -5.1 kcal/mol, Pioglitazone -9.8 kcal/mol, Acarbose -7.6 kcal/mol, Sitagliptin -10.3 kcal/mol, Dapagliflozin -9.4 kcal/mol, on the EPOR protein: Glimepiride 16.0 kcal/mol, Repaglinide 0 kcal/mol, Metformin -3.3 kcal/mol, Pioglitazone -1.4 kcal/mol, Acarbose 14.2 kcal/mol, Sitagliptin -0.2 kcal/mol,

Dapagliflozin -0.2 kcal/mol, on the COX-2 protein, namely Glimepiride -11.0 kcal/mol, Repaglinide -8.1 kcal/mol, Metformin -5.6 kcal/mol, Pioglitazone -9.1 kcal/mol, Acarbose -7.7 kcal/mol, Sitagliptin -9.7 kcal/mol, Dapagliflozin -8.5 kcal/mol. Based on computational analysis, Glimepiride and Sitagliptin exhibit the strongest and most stabel interactions, particularly with the VDR and COX-2 proteins, while Metformin and Dapagliflozin have lower affinities. Drug interactions with target proteins are dominated by hydrogen bonds, hydrophobic, and electrostatic interactions. It is predicted that oral antidiabetic drugs with side effects are Glimepiride and Sitagliptin.

Acknowledgement

This research is self-funded.

Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

REFERENCES

[1] Alnaser, R.I., Alassaf, F.A., Abed, M.N. (2025): Effects of sitagliptin on hematological parameters, erythropoietin levels, and renal and liver functions in patients with type 2 diabetes. – World Academy of Sciences Journal 7(3): 1-8.

[2] Antoniadou, C., Gavriilidis, E., Ritis, K., Tsilingiris, D. (2025): Anemia in diabetes mellitus: Pathogenetic aspects and the value of early erythropoietin therapy. – Metabolism Open 25: 11p.

[3] Hansen, C.S., Lundby-Christiansen, L., Tarnow, L., Gluud, C., Hedetoft, C., Thorsteinsson, B., Hemmingsen, B., Wiinberg, N., Sneppen, S.B., Lund, S.S., Krarup, T., Madsbad, S., Almdal, T., Carstensen, B., Jørgensen, M.E. (2020): Metformin may adversely affect orthostatic blood pressure recovery in patients with type 2 diabetes: Substudy from the placebo-controlled Copenhagen Insulin and Metformin Therapy (CIMT) trial. – Cardiovascular Diabetology 19(1): 1-10.

[4] Luo, P., Qiu, L., Liu, Y., Liu, X.L., Zheng, J.L., Xue, H.Y., Liu, W.H., Liu, D., Li, J. (2020): Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. – American Journal of Tropical Medicine and Hygiene 103(1): 69-72.

[5] Monapati, S., Kaki, P., Gurajapu, M.S., Subhas, P.G., Kudipudi, H.B. (2023): The effects of vitamin D on preventing hyperglycemia and a novel approach to its treatment. – Drugs and Drug Candidates 2(4): 923-936.

[6] Maharani, L., Yugatama, A. (2023): Prevalence of adverse drug reaction in Indonesia: A systematic review. – Journal of Applied Pharmaceutical Science 13(8): 55-67.

[7] Selby, N.M., Taal, M.W. (2020): An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. – Diabetes, Obesity and Metabolism 22(S1): 3-15.

[8] Nakamura, T., Iwanaga, Y., Miyaji, Y., Nohara, R., Ishimura, T., Miyazaki, S., Izumi, T., Inoko, M., Matsuda, M., Inada, T., Tanaka, M., Kondo, H., Nakagawa, Y., Hanatani, A., Yoshiyama, M., Nakagawa, A., Hirai, T., Imagawa, A. (2016): Cardiovascular efficacy of sitagliptin in patients with diabetes at high risk of cardiovascular disease: A 12-month follow-up. – Cardiovascular Diabetology 15(1): 1-10.

[9] Oka, K., Masuda, T., Ohara, K., Miura, M., Morinari, M., Misawa, K., Miyazawa, Y., Akimoto, T., Shimada, K., Nagata, D. (2023): Fluid homeostatic action of dapagliflozin in patients with chronic kidney disease: The DAPA-BODY Trial. – Frontiers in Medicine 10: 1-12.

[10] Suku, C.K., Hill, G., Sabblah, G., Darko, M., Muthuri, G., Abwao, E., Pandit, J., Osakwe, A.I., Elagbaje, C., Nyambayo, P., Khoza, S., Dodoo, A.N., Pal, S.N. (2015): Experiences and lessons from implementing cohort event monitoring programmes for antimalarials in four African countries: Results of a questionnaire-based survey. – Drug Safety 38(11): 1115-1126.