



# An Integrated In Silico and In Vitro Assays of Dipeptidyl Peptidase-4 and $\alpha$ -Glucosidase Inhibition by Stellasterol from *Ganoderma australe*

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Abstract: Background: Ganoderma fungus is rich in terpenoids. These compounds are known for their anti-hyperglycemic activities. However, the study of terpenoids as the secondary metabolite from Ganoderma as a dipeptidyl peptidase-4 (DPP-4) inhibitor remains unexplored. In addition, we examined the  $\alpha$ -glucosidase inhibition activity. Objective: This study aimed to isolate the major terpenoid from non-laccate *Ganoderma* and examined its inhibitor activity on DPP-4 and  $\alpha$ -glucosidase enzymes, and its interaction. Methods: The compound was isolated using column chromatography from Ganoderma australe. The structure of the isolated compound was confirmed by <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectroscopy, while the inhibitory activity was evaluated using an enzymatic assay. The interaction of the isolated compound with DPP-4 and  $\alpha$ -glucosidase enzymes was investigated using an in silico study. Results: The isolated compound was identified as stellasterol;  $IC_{50}$  values for DPP-4 and  $\alpha$ -glucosidase inhibitor were 427.39  $\mu$ M and 314.54  $\mu$ M, respectively. This study revealed that the inhibitory effect of stellasterol on DPP-4 enzyme is through hydrophobic interaction, while the  $\alpha$ -glucosidase enzyme is due to the interaction with six amino acids of the enzyme. Conclusion: Stellasterol is the major component of the steroid from *G. australe*. Enzyme inhibitory assay and in silico study suggest that stellasterol may contribute antidiabetic activity with a mechanism closer to acarbose rather than to sitagliptin.

Keywords: α-glucosidase inhibitor; diabetes mellitus; DPP-4-inhibitor; Ganoderma; in silico; stellasterol

## 1. Introduction

*Ganoderma* is a cosmopolitan woody polypore fungus with a broad distribution in tropical regions, including Indonesia. *Ganoderma* comprises two subgenera based on the pileus surface, the shiny or laccate subgenus (*G. lucidum complex~Ganoderma*), and the non-shiny or non-laccate subgenus (*G. applanatum* complex~*Elfvingia*) [1]. The fruit bodies of *Ganoderma lucidum* have been used for diabetes mellitus treatment as food and folk medicine [2–4]. Moreover, *Ganoderma* is classified as a nutraceutical mushroom similar to cordyceps, shiitake, maitake, chaga, and others for herbal remedies [5]. In contrast, the non-laccate subgenus of *Ganoderma* has received less attention for medical purposes [6].

Antidiabetic drugs that have been released on the market have action mechanisms such as stimulating insulin secretion, delaying digestion and absorption, improving peripheral glucose uptake, suppressing hepatic glucose production, and increasing the sensitivity of insulin receptors [7,8]. The drawbacks of these antidiabetic drugs are hypoglycemia and weight gain [9]. A novel therapeutic approach for diabetes mellitus treatment with weight neutrality uses incretin hormones [8].

Incretin hormones are secreted from the gut and can be classified into two predominant hormones, i.e., glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Food ingestion stimulates the secretion of incretin hormones, then these hormones induce insulin release from pancreatic  $\beta$ -cells, which further reduce the blood glucose [10]. In addition, GLP-1 has some advantages, such as pancreatic  $\beta$ -cell protection, reducing appetite in the brain, and slowing gastric emptying [10,11]. However, the half-life of GLP-1 is short at approximately 2 min, due to the rapid metabolism by the enzyme DPP-4 [12]. According to their structures, DPP-4 inhibitors fall into two categories: peptidomimetic and non-peptidomimetic. Sitagliptin was the first peptidomimetic DPP-4 inhibitor launched, followed by tenegliptin, gemigliptin, anagliptin, and evogliptin during 2012 to 2015. Retagliptin, denagliptin, and gosogliptin are peptidomimetic DPP-4 inhibitors under clinical trials. The peptidomimetic DPP-4 inhibitors do not require peptide scaffolds. Since the peptidomimetic DPP-4 inhibitors were related to enzymatic cleavage, the non-peptidomimetic inhibitors are now being explored. Linagliptin, anagliptin, omarigliptin, and trelagliptin are under clinical trials [13–17].

The  $\alpha$ -glucosidase inhibitors show minimal effects in inducing hypoglycemia and in weight loss. The main downside of  $\alpha$ -glucosidase inhibitors is abdominal discomfort due to its mechanism in preventing the degradation of polysaccharides into monosaccharides. The undigested polysaccharides are digested by bacteria in the colon, thus inducing bloating and diarrhea [18].

This study was aimed to isolate major terpenoid compounds from non-laccate *Ganoderma*. In vitro and in silico assays were conducted to understand the inhibition profile of this compound against DPP-4 and  $\alpha$ -glucosidase enzyme.

## 2. Materials and Methods

## 2.1. Materials

Fresh *Ganoderma australe* was harvested in September 2016 in Bogor Botanical Gardens. The voucher specimens were deposited in Bogor Botanical Gardens (BO22952) and DNA identification was done with GenBank code MK131240. Silica gel 60 (0.063–0.200 mm) for column chromatography and all organic solvents were purchased from Merck. Human DPP-4 enzyme (Product number: D4943), glycine-proline-p-nitroaniline (CAS 103213-34-9) as the chromogenic substrate DPP-4, and Trizma<sup>®</sup> HCl as the DPP-4 buffer were purchased from Sigma. The sodium dihydrogen phosphate monohydrate (NaH<sub>2</sub>PO<sub>4</sub>.H<sub>2</sub>O) and disodium hydrogen phosphate (Na<sub>2</sub>HPO<sub>4</sub>) as  $\alpha$ -glucosidase buffer were purchased from Merck. Para-nitrophenyl  $\alpha$ -D-glucopyranoside (EC. 223-189-3 and CAS 3767-28-0) and  $\alpha$ -glucosidase from *Saccharomyces cerevisiae* (EC. 232-604-7 and CAS 9001-42-7) were obtained from Sigma. The absorbance was measured with an Infinite<sup>®</sup> M200 Pro microplate reader.

## 2.2. Extraction and Isolation

The dried and pulverized fruit bodies of *Ganoderma australe* (3 kg) were extracted exhaustively with hexane using a Soxhlet apparatus. The evaporated hexane extract was subjected to column chromatography to yield seven fractions (A–G) with a stepwise gradient elution of hexane-ethyl acetate (100:0 $\rightarrow$ 0:100 v/v) solvent. Fraction E (1.5 g) was further purified using silica gel column chromatography eluted with hexane-ethyl acetate (100:0 $\rightarrow$  0:50 v/v) to yield five subfractions (E1-E5). Subfraction E3 was further purified by washing with hexane to obtain the isolated compound (Figure 1).



Figure 1. Isolation scheme of stellasterol from *G. australe*.

#### 2.3. Instrumentation

The spectra of <sup>1</sup>H and <sup>13</sup>C-NMR of the isolated compound were recorded on an Agilent spectrometer (<sup>13</sup>C:125 MHz; <sup>1</sup>H:500) with tetramethylsilane (TMS) as the internal standard. The spectrum was measured using deuterated chloroform (CDCl<sub>3</sub>) as a solvent.

#### 2.4. In Vitro Study of DPP-4 Inhibition

Ten milligrams of the isolated compound were diluted in 10 mL Trizma<sup>®</sup> HCl buffer at pH 7.5 (50 mM). Various concentrations of samples at 60, 125, 250, and 500  $\mu$ M and sitagliptin as positive control at 0.5, 1, 2, 4, and 8  $\mu$ M were used. The assay was performed according to Chakrabarti et al. [19] and Al-Masri et al. [20]. Each well contained a mixture of 15  $\mu$ L of DPP-4 enzyme (0.05 U/mL) and 35  $\mu$ L of standard or sample. The mixture was incubated at 37 °C for 10 min as the first incubation. Subsequently, 50  $\mu$ L of substrate 0.2 mM were added to this mixture, followed by the second incubation at 37 °C for 30 min. Finally, to stop the reaction, 25  $\mu$ L acetic acid 25% were added. The absorbance was measured at  $\lambda$  405 nm and the inhibition activity was calculated by the following formula:

% Inhibition = [(Abs control – Abs standard or sample)/Abs control] × 100

## 2.5. In Vitro Study of $\alpha$ -Glucosidase Inhibition

Ten milligrams of the isolated compound were diluted in 10 mL phosphate buffer at pH 6.9. Various concentrations of the isolated compound and 60, 125, 250, and 500  $\mu$ M acarbose were used. The assay was performed according to Munim et al. [21] with slight modifications. The  $\alpha$ -glucosidase enzyme was dissolved in 100 mL phosphate buffer at pH 6.9. Phosphate buffer was prepared by dissolving 1.42 g Na<sub>2</sub>HPO<sub>4</sub> and 1.38 g NaHPO<sub>4</sub>.H<sub>2</sub>O in 100 mL containing 200 mg bovine serum albumin. Each well contained a mixture of 10  $\mu$ L of standard or sample and 25  $\mu$ L of substrate 0.625 mM, followed by first incubation at 37 °C for 10 min. Subsequently, 25  $\mu$ L of an enzyme (0.05 U/mL) were added and incubated for 15 min at 37 °C. One hundred milliliters of sodium carbonate 0.2 mM were used to stop the enzymatic reaction. The absorbance was measured at  $\lambda$  405 nm and the inhibition activity was calculated with the same formula used to measure DPP-4 inhibition.

#### 2.6. In Silico Study

Crystallography of human dipeptidyl peptidase-4 (PDB: 1X70) complex with sitagliptin and  $\alpha$ -glucosidase from *Saccharomyces cerevisiae* (PDB: 3W37) complex with acarbose were obtained from the Protein Data Bank. The structure of the isolated compound was downloaded from the PubChem database. Preparation of the ligand and the protein was performed using the AutoDock Tools 1.5.6 program (ADT). The interaction pattern between the ligand and the receptor was studied using the Lamarckian genetic algorithm (LGA). Docking studies were carried out using AutoDock Tools v.1.5.6 embedded in MGL Tools [22]. The grid box of sitagliptin was adjusted at *x* 41.376; *y* 51.2; *z* 36.2 and the grid box of acarbose was adjusted at *x* 0.699; *y* –1.87; *z* –23.212.

#### 2.7. Statistical Analysis

All inhibitory data are expressed as mean  $\pm$  SD (n = 3). The IC<sub>50</sub> data were calculated using GraphPad Prism 8.0.1 software free trial with non-linear regression sigmoidal dose-response.

## 3. Results and Discussion

## 3.1. Structure Elucidation

The <sup>1</sup>H NMR spectrum of the isolated compound clearly showed six methyl signals at  $\delta$  0.54 (3H, s, H-18); 0.79 (3H, s, H-19); 1.01 (3H, d/s, J = 5.5 Hz, H-21); 0.91 (3H, d, J = 5 Hz, H-24"); 0.81 (3H, d, J = 15 Hz, H-26); 0.81 (3H, s, H-27) ppm. The <sup>13</sup>C-NMR revealed the presence of 28 carbon signals ascribed to six methyls at  $\delta$  12.1 (C-18); 13.1 (C-19); 21.2 (C-21); 17.7 (C-24"); 19.8 (C-26); 20.1 (C-27) ppm, eight methylenes at  $\delta$  37.3 (C-1); 31.6 (C-2); 38.1 (C-4); 29.8 (C-6); 21.7 (C-11); 39.6 (C-12); 23.0 (C-15); 28.2 (C-16) ppm, and eleven methines at  $\delta$  71.2 (C-3); 40.6 (C-5); 117.1 (C-7); 49.6 (C-9); 55.3 (C-14); 56.1 (C-17); 40.4 (C-20); 135.9 (C-22); 132.1 (C-23); 43.0 (C-24); 33.2 (C-25) ppm. It also showed the presence of two double bonds signals at  $\delta$  117.6 (C-7); 132.1 (C-23); 135.9 (C-22); and 139.7 (C-8) ppm (Figure 2). By comparison with published NMR data, the isolated compound was identified as stellasterol [23,24].



Figure 2. Stellasterol isolated from Ganoderma australe.

#### 3.2. Assay of DPP-4 and $\alpha$ -Glucosidase Inhibition

Our previous study showed that hexane extract had the highest activity to inhibit  $\alpha$ -glucosidase enzyme followed by ethyl acetate and methanol extract (data not shown). These results suggest that there are responsible compounds as  $\alpha$ -glucosidase inhibitor present in hexane extract. Based on extraction-guided activity, we decided to isolate the hexane extract then examined two different inhibition enzyme mechanisms. Our isolation revealed that stellasterol was the major compound from the hexane extract.

Stellasterol showed DPP-4 inhibition activity with IC<sub>50</sub> at 427.39  $\mu$ M, while sitagliptin as the positive control had IC<sub>50</sub> 0.73  $\mu$ M. Sitagliptin showed much stronger activity against DPP-4 enzyme than stellasterol. As the  $\alpha$ -glucosidase inhibitors, stellasterol and acarbose were 314.54  $\mu$ M and 207.87  $\mu$ M, respectively. By comparing the standards, it seems that the activity of stellasterol was more similar to acarbose rather than sitagliptin as a hypoglycemic agent. These results were studied using in silico interaction.

#### 3.3. Stellasterol In Silico Study for DPP-4 Enzyme

The in silico approach was performed to predict the protein–ligand binding pose between stellasterol, either with DPP-4 or  $\alpha$ -glucosidase enzyme. The root mean square (RMSD) of 0.50 Å was gained for stellasterol with the native ligand extracted from the DPP-4 enzyme, while RMSD score for stellasterol in comparison to the origin of the  $\alpha$ -glucosidase enzyme was 1.18 Å. The most negative docking score was chosen to be used in analyzing pose interaction between ligand and receptor [25].

Docking simulation of stellasterol into the DPP-4 cavity revealed that the main interaction was hydrophobic. Stellasterol filled the hydrophobic cavity involving Trp659, Tyr547, Tyr631, Tyr662, Tyr666, Phe357, Val656, and Val711 (Table 1). Marvanita and Patel [26] suggested that these amino acid residues were the natural hydrophobic cavity of human DPP-4 (Table 2). Furthermore, linagliptin had  $\pi$ - $\pi$  interactions in addition to Tyr547 and Trp629 residues compared to alogliptin. These additional interactions are believed to be the leading factor to elevate the potential for linagliptin compared to alogliptin [27]. Arulmozhiraja et al. [28] proposed that the interaction with Glu206 and Glu205 through hydrogen bonds in sitagliptin, alogliptin, linagliptin, and teneligliptin inhibitors are the first specifications for DPP-4 inhibitor beside Tyr547, Trp629, Tyr666, and Phe357. In addition, the interaction with S2' is important and interaction with the S2 extensive can elevate not only the potency but also the selectivity. Furthermore, larger inhibitors that fulfill the hydrophobic cavity could elevate the inhibitory potential and stabilize the ligand–receptor complex [28,29]. Stellasterol only interacts with Tyr547 in  $\pi$ -alkyl interaction and other interactions mostly through hydrophobic bonds, suggesting its lower capacity to bind DPP-4 enzyme.

Kalhotra et al. [30,31] examined the profile for the addition of hydroxyl groups to inhibit the DPP-4 enzyme. Their results showed that galangin (a flavonoid with two hydroxyl groups) gives higher inhibition than chrysin (a flavonoid with two hydroxyl groups). Saleem et al. [32] also revealed that quinovic acid has an IC<sub>50</sub> value of 30.7  $\mu$ M, whereas the addition of two glucose moieties in quinovic acid elevate the activity (IC<sub>50</sub> 23.5  $\mu$ M).

Stellasterol has only one free hydroxyl group at C-3; perhaps this is caused by the lower inhibition of the DPP-4 enzyme in comparison to the previously structure. Stellasterol, a steroid derivative, has a non-polar structure in nature exposing domination of alkyl and proton aliphatic groups. Conversely, sitagliptin as the positive control contains fluoro and amine capable of forming hydrogen bonds with some amino acids in the DPP-4 cavity. A hydroxyl group of stellasterol interacts through hydrogen bonding with amino acid Tyr585 in the DPP-4 pocket. This amino acid Tyr585 is a different type to the amino acids that bind with sitagliptin, Glu205, Glu206, Arg125, Arg358, and Asn710. The hexane extract showed higher inhibition of DPP-4 enzyme than stellasterol, indicating the activity against DPP-4 enzyme may not be contributed by stellasterol as the major isolate. According to Arulmozhiraja et al. [28], stellasterol fulfills the second and third specifications for DPP-4 inhibitor.

#### 3.4. Stellasterol In Silico Study for $\alpha$ -Glucosidase Enzyme

The docking result revealed that acarbose, an oligosaccharide, is surrounded by many hydroxyl groups that are able to form a hydrogen bond with amino acid residues, such as Arg552, Asp568, Asp357, His626, Asp232, Asn237, and Ala234 (Figure 3).

In the  $\alpha$ -glucosidase cavity, a hydroxyl group position at C-3 of stellasterol interacted with Asn237 through a hydrogen bond similar to acarbose as a positive control. Tagami et al. [33] proposed that Asn237 was one of the residues that play a role in the long-chain specificity inside the N-loop. This interaction possibly has a role in increasing the activity of stellasterol against  $\alpha$ -glucosidase rather than DPP-4 enzyme. In addition, stellasterol binds with the same two amino acids Trp329 and Phe601, similar to acarbose in the hydrophobic pocket. Stellasterol also binds with His626, Ala234, and Met470 in  $\pi$ -alkyl interaction (Table 3).



**Figure 3.** The binding mode 2D view of the  $\alpha$ -glucosidase enzyme with stellasterol and acarbose.

Several terpenoid compounds have been tested as  $\alpha$ -glucosidase inhibitors, including ursolic acid, 3 $\beta$ -hydroxy-11-ursen-28,13-olide, and ursonic acid. These compounds demonstrated IC<sub>50</sub> 8.38, 203.76, and 100.99  $\mu$ M. Those compounds showed higher inhibitory activity compared to stellasterol. These might be due to the presence of carbonyl or the additional hydroxyl groups, or the carboxylic acid group, which leads to the stronger interaction with  $\alpha$ -glucosidase enzyme [34].

Four triterpenoids from *Psidium guajava* leaves, namely trihydroxyopsidiumlanostenoic acid, 12β-hydroxypsidiumlanostenoic acid, psidiumlanostenoic acid glucoside, and psidiumlanostenoic acid, as shown in Figure 4, have been tested in vivo for antidiabetic activity. The administration of 50 mg/kg of these isolate compounds for 1 week in diabetic rats model showed blood glucose levels of 142.50, 154.50, 165.67, and 172.17 mg/dL, respectively. However, the normal control rat and the diabetic control rat showed 87.66 and 327.33 mg/dL blood glucose levels after 1 week [35].



**Figure 4.** Lanosterol derivates as  $\alpha$ -glucosidase inhibitor [35].

Although in vitro study showed that the IC<sub>50</sub> as an  $\alpha$ -glucosidase inhibitor is relatively high, another study reported that similar compounds have the capacity to reduce the blood glucose level. Therefore, with stellasterol it may contribute to the anti-diabetic activity in *G. australe*.

Ligand	Hydrogen Bond								Hydrophobic Bond						
0	Glu206	Glu205	Arg358	Arg125	Asn710	Tyr585	Tyr631	Tyr547	Tyr666	Tyr662	Val711	Val656	Trp659	Phe357	
Stellasterol	-	-	-	-	-	+	π–alkyl	π–alkyl	π–alkyl	π–alkyl	Alkyl–alkyl	Alkyl–alkyl	π–alkyl	π–alkyl	
Sitagliptin	+	+	+	+	+	-	-	-	π-π	π-π	-	-	-	π–π	

**Table 1.** Interaction of stellasterol and sitagliptin with the binding pocket of the human DPP-4 enzyme.

Table 2. Amino acid residues in the active site of the DPP-4 enzyme [28]	•
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Amino Acid Residues			Pocket				
Allillo Acia Residues —	S2′	S1′	S1	S2	S2 Ext		
	Trp629	Tyr547	Tyr666	Arg125	Phe357		
	His740	Tyr631	Ser630	Arg669	Arg358		
	Ser630	Phe357	Val656	Glu205	Ser209		
	Tyr547	Pro550	Trp659	Glu206	Val207		
	ý	Tyr666	Tyr662	Phe357			
		,	Val711	Arg358			
			Asn710	0			

**Table 3.** Interaction if stellasterol and acarbose with the binding pocket of the  $\alpha$ -glucosidase enzyme.

Ligand	Hydrogen Bond									Hydrophobic Bond								
	Arg552	Asp568	Asp367	His626	Asp232	Asn237	Ala234	Ile358	Ile233	Ile396	Trp467	Trp329	Trp432	Trp329	Phe601	Phe236	Ph3476	Met470
Stellasterol	-	-	-	π–alkyl	-	+	π–alkyl	+	-	+	-	+	+	-	+	+	-	π–alkyl
Acarbose	+	+	+	+	+	+	+	-	-	-	-	+	-	-	+	-	-	+

## 4. Conclusions

The in silico approach helps one to understand and support the invitro result. According to invitro and in silico results, stellasterol was more likely well-fitted as an  $\alpha$ -glucosidase inhibitor rather than a DPP-4 inhibitor.

**Author Contributions:** S.S. designed the experiments and reviewed the manuscript. K.B., Y.B.P., and K.R.W. collected the mushroom, performed extraction and isolation, performed the experiments, and analyzed the NMR results. K.B. and J.J. performed the in silico experiment. K.B. wrote the manuscript.

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