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RESEARCH ARTICLE

Antidiabetic and Antioxidant Potential of GancidinW from *Streptomyces Paradoxus* VITALK03

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Abstract:

Background:

The aim of the present study was to analyse the antidiabetic and antioxidant potential of GancidinW (GW) extracted from *Streptomyces paradoxus* VITALK03.

Materials and Methods:

Antidiabetic potential of GW was evaluated by assay of α -amylase and α -glucosidase inhibitory activity; haemoglobin glycosylation and yeast glucose uptake. The antioxidant potential of GW was assessed by 2,2-Diphenyl-1-picrylhydrazyl (DPPH) assay, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical cation decolorization assay and superoxide assay. The inhibition of α -amylase and α -glucosidase by GW was also studied by *in Silico* molecular docking analysis.

Results:

GW (1mg/ml) showed 69.32% of α -amylase and 54.04% of α -glucosidase inhibitory activity. GW (1mg/ml) prevented haemoglobin glycosylation up to 30.92% and the glucose uptake by yeast cells was increased up to 64.38%. The binding interaction GW with α -amylase showed the least free binding energy of -6.09Kcal/mol and -7.53Kcal/mol with α -glucosidase by docking studies. GW also demonstrated moderate antioxidant activity in all the antioxidant assays performed.

Conclusion:

The results of this study suggests that the antidiabetic and antioxidant potential of GW can be probed further to develop GW as effective antidiabetic agent.

Keywords: GancidinW, Antioxidant, Antidiabetic activity, α -amylase, α -glucosidase, Glycosylation.

1. INTRODUCTION

Actinomycetes are gram positive, saprophytic and filamentous bacteria belonging to the order *Actinomycetales* and the family Actinomycetaceae [1, 2]. Among the various prokaryotes, actinomycetes are one of the economically important bacteria and the genus *Streptomyces* are known for producing several bioactive compounds. Actinomycetes are prolific producers of numerous bioactive compounds and new chemical entities. Out of 23000 bioactive compounds isolated from the microorganisms, more than 10000 bioactive compounds were from actinomycetes, among them, 7600 were isolated from *Streptomyces* species [3]. Antibacterial, antifungal, antiviral, anticancer and antimalarial activities of bioactive compounds extracted from actinomycetes have already been reported [4]. However, in the recent years, the rediscovery of known bioactive compounds in terrestrial actinomycetes have increased and therefore researchers have shown increased interest in exploring marine actinomycetes. The marine ecosystem offers a greater diversity which is

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vastly different from the terrestrial environment. Despite the recent success with the discovery of novel bioactive compounds from the marine actinomycetes, only 1% of them have been estimated to be identified [5] and still several compounds yet to be identified. Several pathogens developing resistance to current drugs available in the market; and cancer cells becoming resistant to existing class of cancer drugs are currently considered as a major challenge for scientists worldwide for controlling drug resistance pathogens and cancer. Screening of marine microbes for novel bioactive compounds and new chemical entities is on war footing to combat the microbial drug resistance and drug resistance by cancer cells. Marine actinomycetes isolated from unexplored and underexplored regions can offer new and effective bioactive compounds [6].

India is one of the 6 countries with leading number of diabetes patients and the number is increasing every year. According to World Health Organization report, India had 69.1 million diabetes cases in 2015. The people living in the urban India, have a high prevalence of diabetes and also, majority of urban population are at the risk of acquiring diabetes, due to their impaired glucose tolerance [7, 8]. It was already reported that diabetes has a great impact on the future of the Indian economy [9]. The rapid increase in diabetic population in India is of great concern which needs to be addressed. The continuous increase of diabetic population warrants for the search of new and effective antidiabetic agents. Although several antidiabetic drugs are available in the market, the side effects and cost of these medicines makes it unaffordable and difficult for long-term use. The prevailing situation in India and other countries raise the demand for developing a cost effective antidiabetic drug, with no major side effects, that could benefit the entire diabetic population.

The aim of the work was to study the antidiabetic and antioxidant potential of GW extracted from marine *Streptomyces paradoxus* sp. VITALK03. The inhibitory potential of GW on α -amylase and α -glucosidase was also validated by molecular docking analysis.

2. MATERIALS AND METHODS

2.1. Isolation of Marine Actinomycetes

Marine actinomycetes were isolated from Rameswaram and Dhanushkodi coastal soil samples by serial dilution and spread plate method. All isolates were screened for bioactivity. The chloroform extract prepared from the potential isolate *Streptomyces paradoxus* sp. VITALK03 was subjected to purification by silica gel column chromatography. The extraction, purification and identification of the active secondary metabolite GW was already been reported [3, 10].

2.2. DPPH Assay

DPPH assay (1, 1-diphenyl 2-picryl hydrazyl) was performed based on the method described by Von Gadow *et al.* (1997) [11]. Two mL of methanolic solution of DPPH (6×10^{-5} M) was added to methanolic solution of the test sample (50 μ l) (methanolic solution of GW (200, 400, 600, 800 and 1000 μ g/ml) was prepared and used, Quercetin was used as a standard. The DPPH scavenging effect (decrease in absorbance at 515 nm) of GW (for all the concentrations), quercetin and blank was recorded after 16 min of incubation. The percentage inhibition of the DPPH radicals by GW was calculated according to the formula of Yen and Duh (1994) [12].

$$\text{Scavenging Activity (\%)}: [(A-B)/A] \times 100$$

Where 'A' is the absorbance of DPPH solution, and 'B' is the absorbance of GW [11].

2.3. ABTS Assay

The free radical scavenging potential of GW was tested using 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical cation decolorization assay [13]. Aqueous solution of ABTS (7 mM) was prepared and ABTS radical cation (ABTS^{•+}) was produced by reacting ABTS stock solution with 2.45 mM potassium persulfate (final concentration) and allowing the mixture to stand in the dark at room temperature for 12 h before use. To study the radical scavenging activity of GW, the ABTS^{•+} solution was diluted with absolute ethanol to get the absorbance of 0.70 (± 0.02) at 734 nm and equilibrated at 30°C. After addition of 2.0 mL of diluted ABTS^{•+} solution ($A_{734 \text{ nm}} = 0.700(\pm 0.02)$) to GW (20 μ L) (200, 400, 600, 800 and 1000 μ g/ml), the absorbance was recorded at 30°C exactly 6 min after initial mixing (A_t). Reagent blank was also used and the reading was taken (A). Butylated hydroxyl toluene was used as a standard. The percentage inhibition of absorbance at 734 nm was calculated using the above formula and decrease of the absorbance between A and A_t .

$$PI = [(A_{C(0)} - A_{A(t)}) / A_{C(0)}] \times 100$$

Where $A_{C(0)}$ is the absorbance of blank at $t = 0$ min; and $A_{A(t)}$ is the absorbance of GW at $t = 6$ min [13].

2.4. Superoxide Anion Radical Scavenging Activity

Superoxide radicals were generated by the method of Beauchamp and Fridovich (1971) described by Zhishen et al (1999) with slight modification [14]. The superoxide radicals generated from riboflavin and methionine were illuminated and assayed by the reduction of nitroblue tetrazolium (NBT) to form a blue formazan (NBT^{2+}). All solutions were prepared by using 0.05 M phosphate buffer (pH 7.8). The photo-induced reactions were performed using fluorescent lamps (20 W). The total volume of the reaction mixture was 3 mL and the concentrations of the riboflavin, methionine, and NBT were 1.33×10^{-5} , 4.46×10^{-5} and 8.15×10^{-8} M respectively. The reaction mixture containing different concentrations of the GW (200, 400, 600, 800 and 1000 μ g/ml) was used to study superoxide radical scavenging activity. The reactant was illuminated at 25°C for 40 min. The photochemically generated superoxide radical from the reaction mixture reduce the NBT to form blue formazan. Tannic acid (15 μ g/ mL) was added to the reaction mixture, in which superoxide was scavenged, thereby inhibiting the NBT reduction. The un-illuminated reaction mixture was used as a blank. The absorbance was measured at 560 nm. The decrease in absorbance of the reaction mixture indicates the increased superoxide anion scavenging activity of GW. The percentage inhibition of superoxide anion generation was calculated by using the following formula:

$$O_2 \text{ scavenging effect (\%)} = (1 - AS/AC) \times 100$$

Where AC is the absorbance of the GW and AS is the absorbance of tannic acid [14].

2.5. Assay of α -amylase Inhibition

Alpha-amylase hydrolyses alpha-bonds of a large alpha-linked polysaccharide such as glycogen and starch to yield glucose and maltose. Alpha-amylase inhibitory activity was assayed by starch-iodine method [15, 16] with some modifications. In alpha-amylase inhibition assay 1 ml of substrate- potato starch (1% w/v), 1 ml of GW (250, 500, 750 and 1000 μ g/ml), 1 ml of alpha-amylase enzyme (1% w/v) and 2 ml of acetate buffer (0.1 M, 7.2 pH) was added. Acarbose was used as standard and potato starch solution, alpha-amylase solution GW was prepared in 0.5 M acetate buffer. The above mixture was incubated for 1 hr. Then, 0.1 ml iodine-iodide indicator (635 mg iodine and 1 gm potassium iodide in 250 ml distilled water) was added to the mixture. Absorbance was measured at 565 nm in UV-Visible spectrophotometer.

$$\% \text{ inhibition} = [(Ac-As)/Ac] \times 100$$

Where Ac is the absorbance of the control (containing all reagents except GW), and As is the absorbance of GW [16].

2.6. Assay of α -glucosidase Inhibition

The α -glucosidase inhibitory activity of GW was carried out by the method of Dahlqvist (1964) [17] with slight modification [18]. The mouse small intestine homogenate was used as a α -glucosidase solution to measure the inhibitory effect. After fasting for 20 h, the small intestine (the portion below the duodenum and above the cecum) was cut, rinsed with ice-cold saline, and homogenized with 12 ml of maleate buffer (100 mM, pH 6.0). The homogenate was used as the source of α -glucosidase solution. The assay mixture consisted of 100 mM maleate buffer (pH 6.0), 2% (w/v) each sugar substrate solution (100 μ l), and GW (200–1000 μ g/ml). It was preincubated for 5 min at 37°C, and the reaction was initiated by adding the crude α -glucosidase solution (50 μ l), followed by incubation for 10 min at 37°C. The glucose released in the reaction mixture was determined with the commercially available glucose estimation kit (Span Diagnostic Ltd., Mumbai, India) the rate of carbohydrate decomposition was calculated as the percentage ratio to the amount of glucose obtained when the carbohydrate was completely digested. The rate of inhibition was calculated by the following formula:

Inhibition (%) = [(amount of glucose produced by the positive control) - (amount of glucose produced by the addition of GW) - (glucose production value in blank) / (amount of glucose produced by the positive control)] x 100

2.7. Non-Enzymatic Glycosylation of Haemoglobin

Antidiabetic activity of GW was investigated by estimating the degree of non-enzymatic haemoglobin

glycosylation, measured calorimetrically at 520 nm. Glucose (2%), haemoglobin (0.06%) and gentamycin (0.02%) solutions were prepared in phosphate buffer 0.01 M, pH 7.4. The above solutions (1 ml each) were mixed. GW was weighed and dissolved in DMSO to obtain a stock solution of 200-1000 µg/ml and 1 ml of each concentration was added to the above mixture. The above mixture without the GW was also prepared and kept as control. The mixture was incubated in dark at room temperature for 72 hrs. The degree of glycosylation of haemoglobin was measured calorimetrically at 520 nm.

$$\text{Inhibition (\%)} = ((Ac-As)/Ac) \times 100.$$

Where Ac is the absorbance of control; As is the absorbance of GW.

2.8. Glucose Uptake in Yeast Cells

Yeast cells were prepared as described previously [18]. Baker's yeast was washed with distilled water by repeated centrifugation (3,000×g; 5 min) until the supernatant fluids were clear and finally 10% (v/v) suspension was prepared in distilled water. Different concentrations of GW (1–5 mg) were added to 1 mL of glucose solution (5, 10 and 25 mM) and incubated together for 10 min at 37°C. Reaction was started by adding 100 µl of yeast suspension, vortexed and further incubated at 37°C for 60 min. After 60 min, the tubes were centrifuged (2500 g for 5 min) and glucose was estimated in the supernatant. Metronidazole was taken as a standard drug. The percentage increase in glucose uptake by yeast cells was calculated using the following formula

$$\text{Glucose uptake (\%)} = ((Ac-As)/Ac) \times 100.$$

Where Ac is the absorbance of control (containing all reagents except GW); As is the absorbance of GW [15, 18].

3. RESULTS

3.1. Antioxidant Activity of GW

3.1.1. DPPH Assay

GW (1000 µg/ml) demonstrated a moderate (34%) antioxidant activity (free radical inhibitory activity) in DPPH assay. The results of DPPH radical scavenging activity of GW in comparison with the quercetin (standard) is shown in Fig. (1).

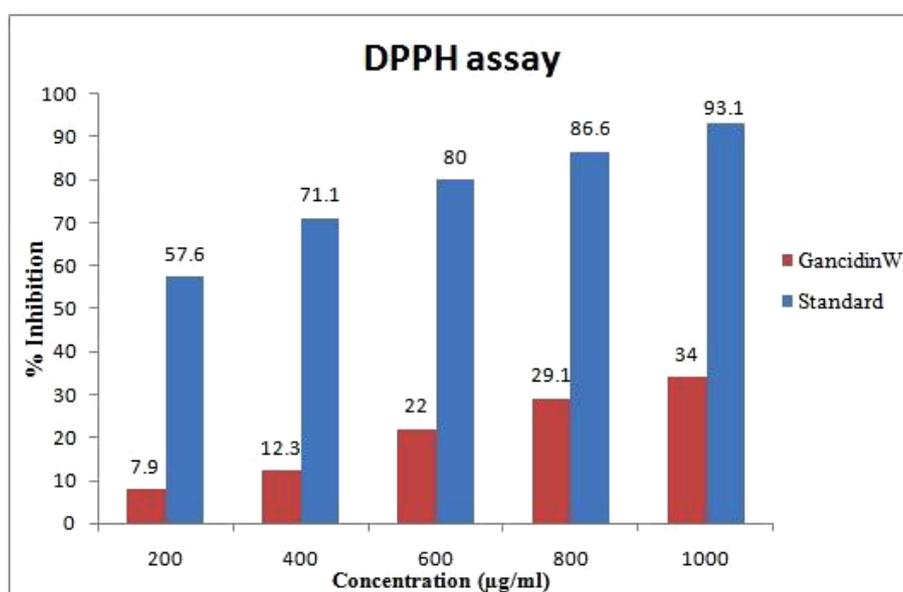


Fig. (1). DPPH (1, 1- diphenyl 2-picryl hydrazyl) scavenging activity of GW from *Streptomyces paradoxus* VITALK03.

3.1.2. ABTS Assay

GW (1000 μ g/ml) demonstrated a moderate (48%) antioxidant activity in ABTS assay. The ABTS radical cation decolorization activity of GW in comparison with butylated hydroxyl toluene (standard) is shown in Fig. (2).

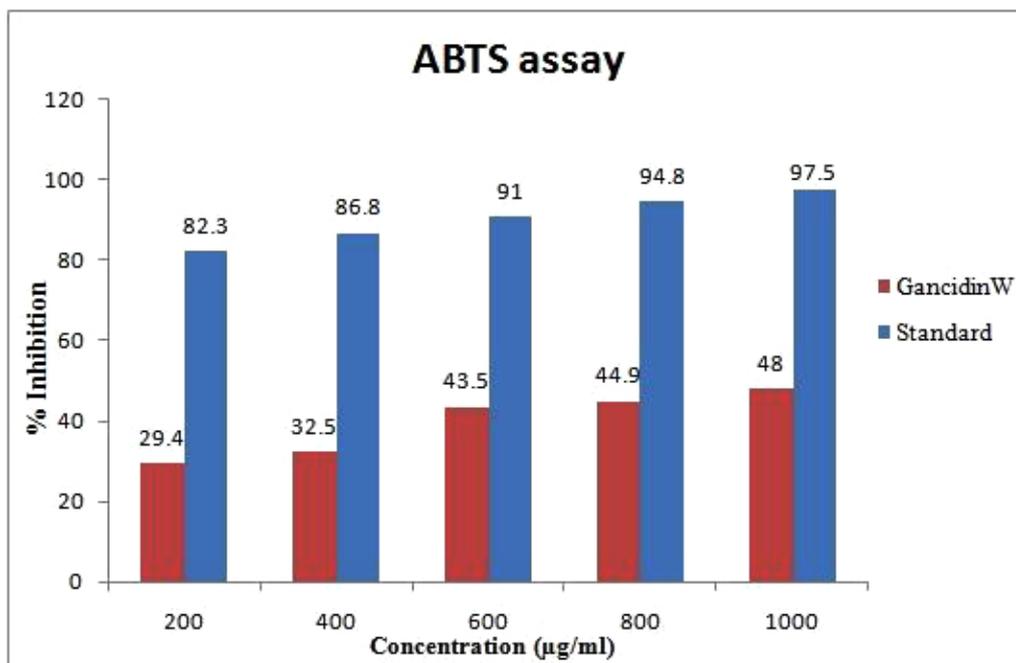


Fig. (2). ABTS (2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) free radical scavenging activity of GancidinW.

3.1.3. Superoxide Assay

GW (1000 μ g/ml) demonstrated a significant (61.5%) antioxidant activity (free radical inhibition) in superoxide assay. The results of superoxide assay for GW in comparison with tannic acid (standard) is shown in Fig. (3).

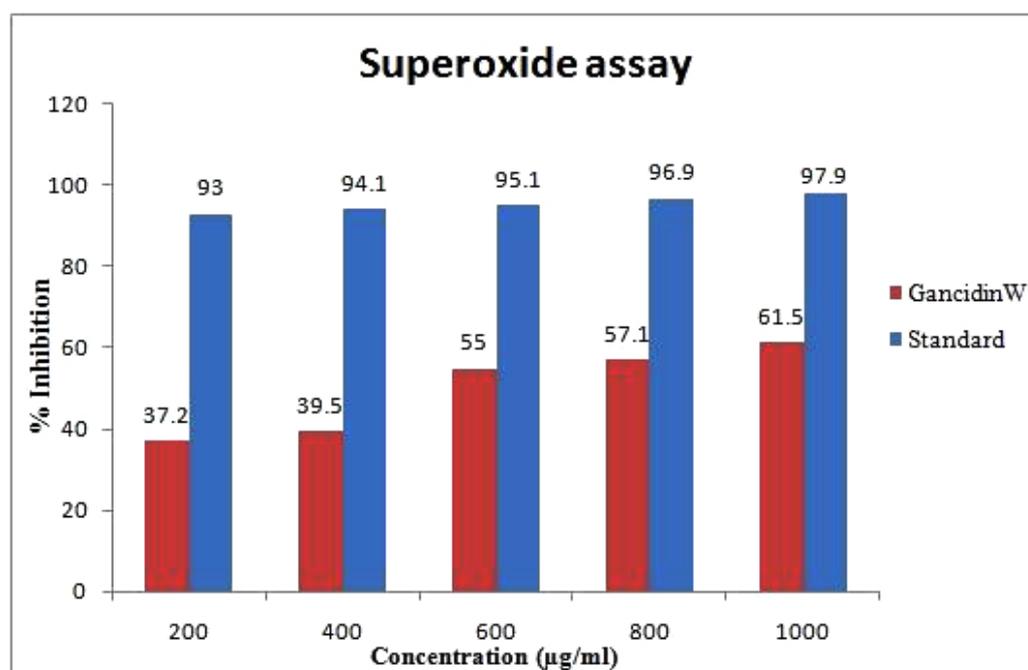


Fig. (3). Superoxide radical scavenging activity of GancidinW.

3.2. Antidiabetic Activity of GW

3.2.1. α -amylase Inhibition

GW (1000 μ g/ml) showed a significant (69.32%) inhibition of alpha-amylase activity. The alpha-amylase inhibitory activity at various concentrations of GW is shown in Fig. (4).

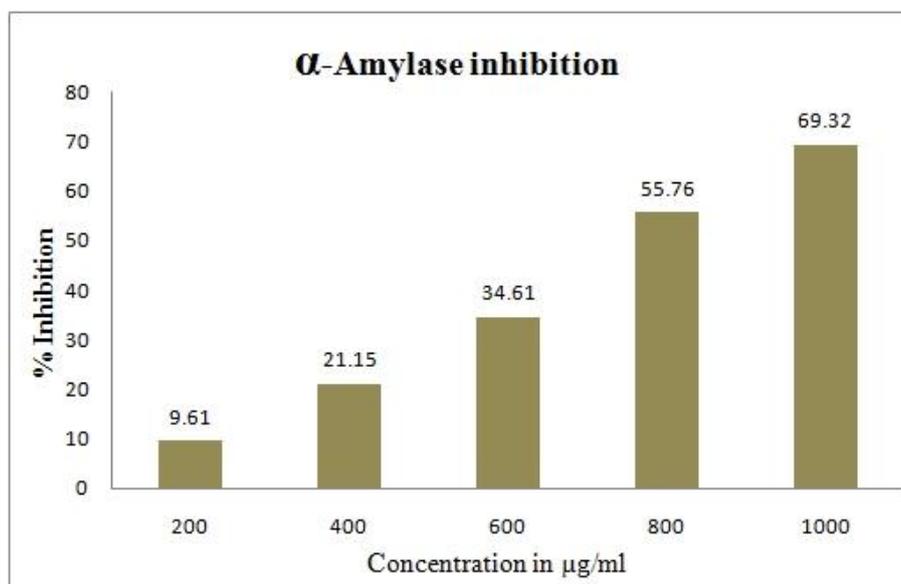


Fig. (4). Alpha-amylase inhibitory activity of GancidinW.

3.2.2. α -glucosidase Inhibition

GW (1000 μ g/ml) showed significant (54.05%) alpha-glucosidase inhibitory activity. The alpha-glucosidase inhibitory activity at various concentrations of GW is shown in Fig. (5).

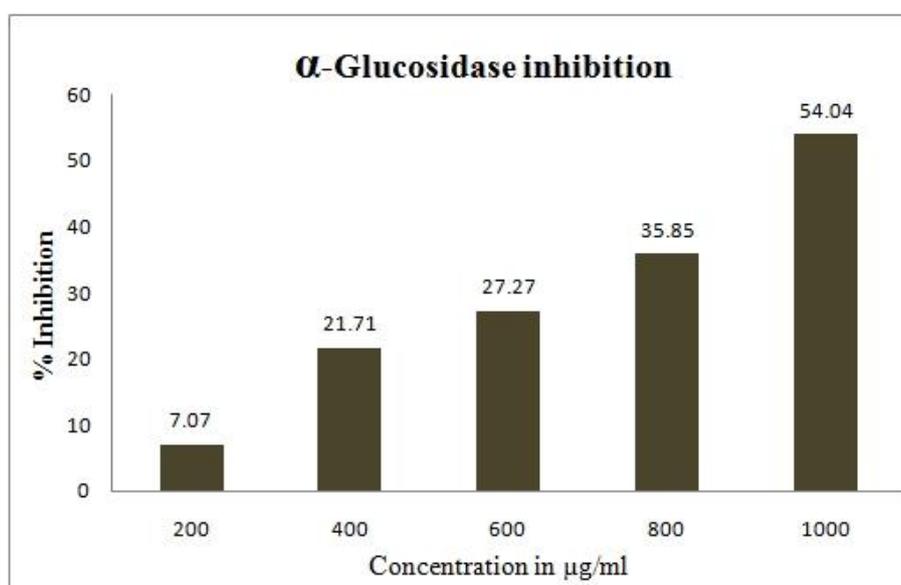


Fig. (5). Alpha-glucosidase inhibitory activity of GancidinW.

3.2.3. Glycosylation of Haemoglobin

GW (1000 μ g/ml) prevented the haemoglobin glycosylation by (30.9%). Inhibition of haemoglobin glycosylation at various concentrations of GW is shown in Fig. (6).

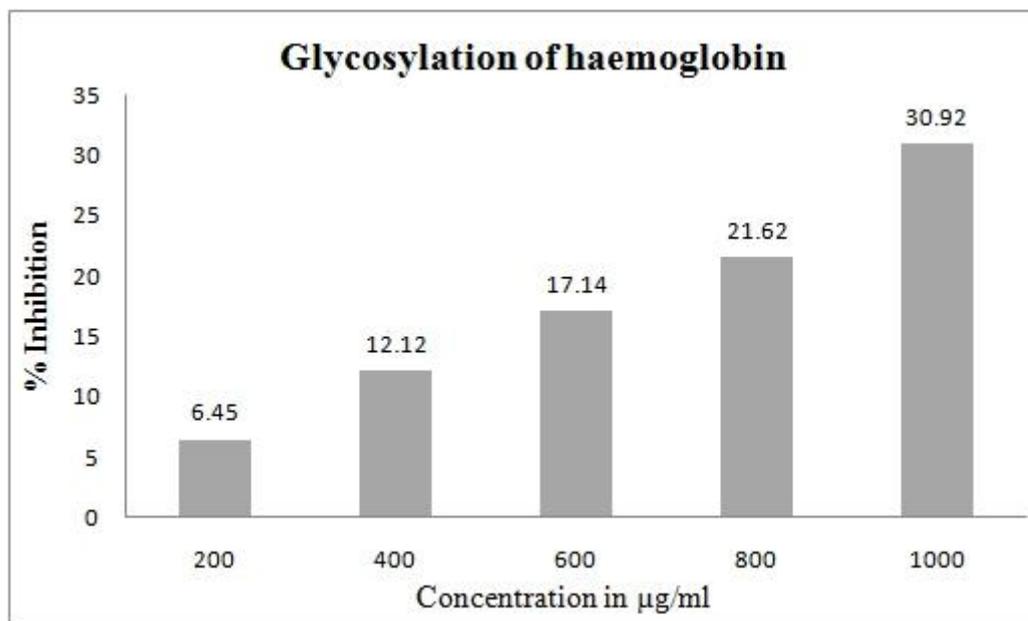


Fig. (6). Effect of Gancidin W on haemoglobin glycosylation.

3.2.4. Glucose Uptake by Yeast Cells

GW (1000 μ g/ml) significantly increased (64.3%) the uptake of glucose by yeast cells. Increase in glucose uptake by yeast cells at various concentrations of GW is illustrated in Fig. (7).

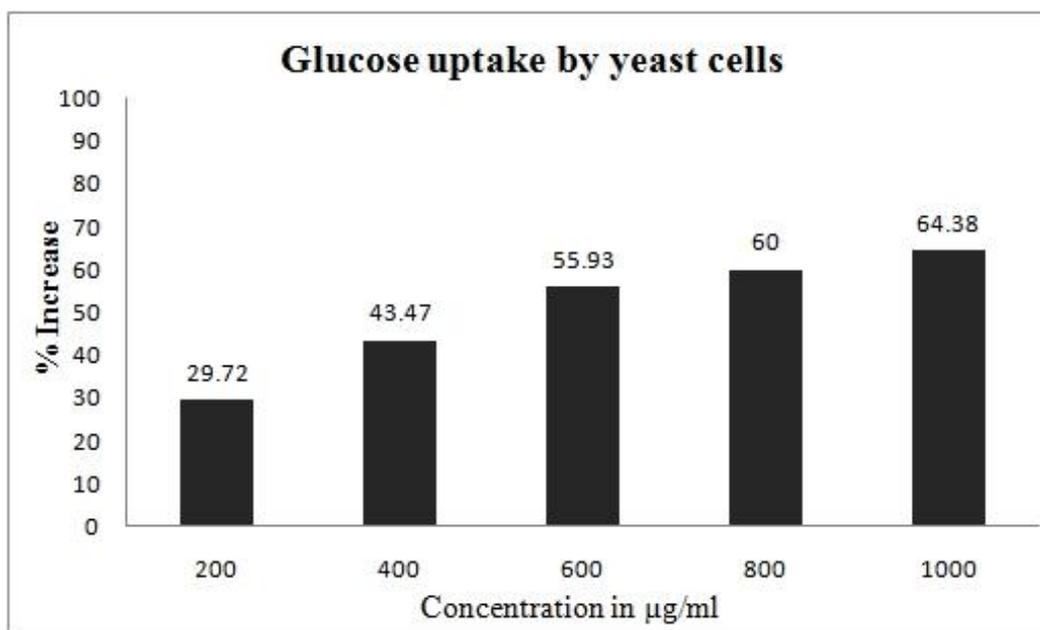


Fig. (7). Effect of Gancidin W on glucose uptake by yeast cells.

3.3. *In Silico* Protein-Ligand Docking Analysis

The ability of GW to inhibit α -amylase and α -glucosidase were studied by *in Silico* protein-ligand docking analysis using AutoDock 4.2. GW interaction with α -amylase showed a least free binding energy of -6.09 Kcal/mol and inhibition constant (K_i) of 34.63 μ M and formed 1 hydrogen bond with LYS-200 (2.72Å). Interaction of GW with α -amylase is shown in Fig. (8).

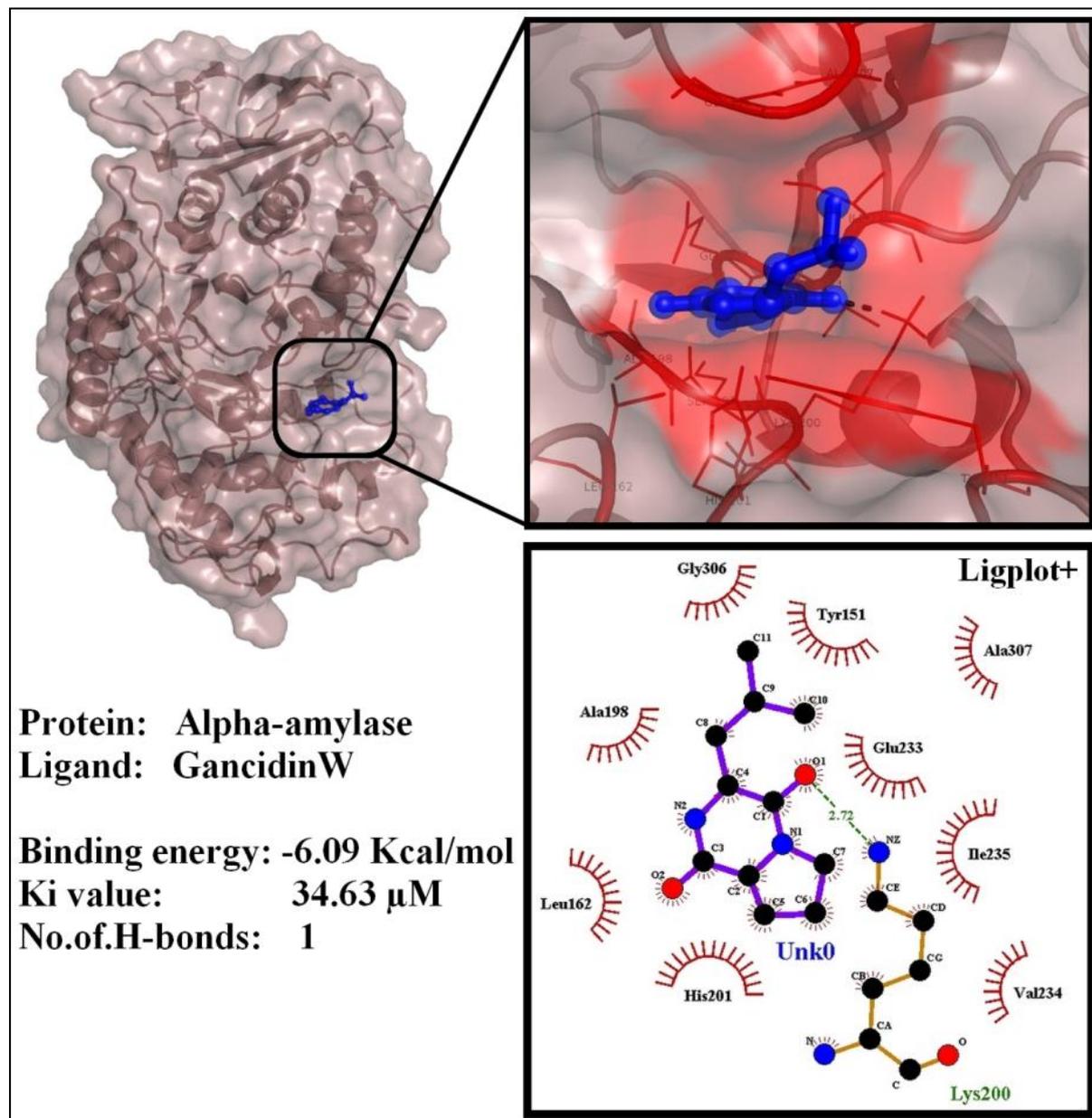


Fig. (8). Interactions of GancidinW with alpha-amylase enzyme.

In Silico analysis revealed the interaction between GW and α -glucosidase enzyme. It showed the least free binding energy of -7.53 Kcal/mol and K_i value of 3.04 μ M and formed 2 hydrogen bonds with ILE-13 (2.71Å) and TYR-46 (3.20Å). Interaction of GW and α -glucosidase is shown in Fig. (9).

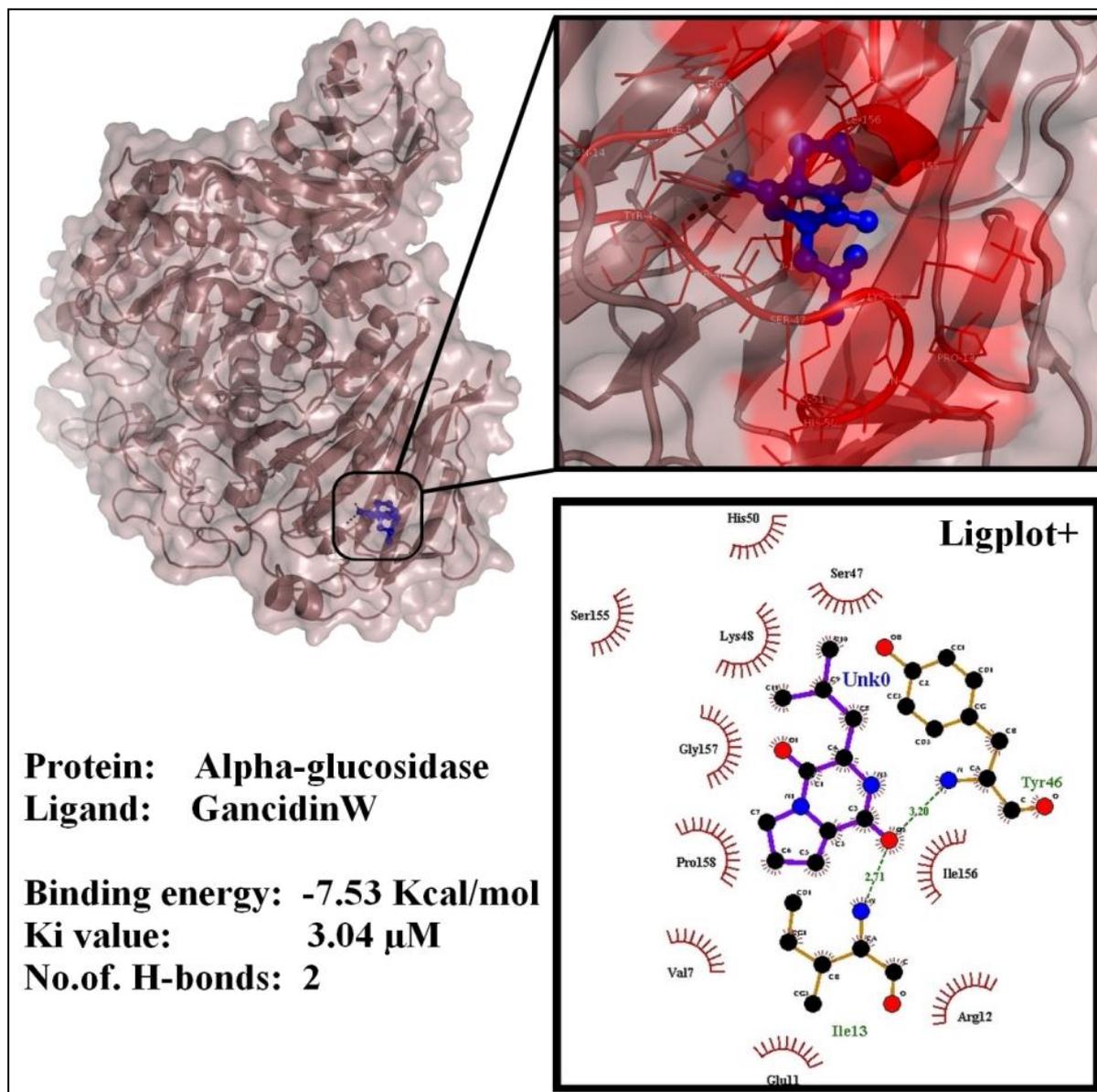


Fig. (9). Interactions of GancidinW with alpha-glucosidase enzyme.

4. DISCUSSION

GW extracted from *Streptomyces paradoxus* sp. VITALK03 showed significant antidiabetic and antioxidant activity. Antioxidant property helps to reduce the oxidative stress in the host, generated due to the metabolic disorder or the drug interactions within the host. The antioxidant property of compounds helps to control the oxidative stress generated by non-specific reactions. The observed free radical scavenging activity of GW would be helpful to reduce the oxidative stress generated during non-specific interactions. Since GW demonstrated moderate antioxidant activity with high percentage of superoxide radical scavenging activity, it can be used as potential antioxidant agent.

Diabetes mellitus is one of the major health disorders in developing countries affects people of all age groups. Till date there is no effective remedy available for effective control and management of diabetes mellitus except administration required dose of insulin. Several enzymes are involved in carbohydrate metabolism, which serves as the target for controlling hyperglycemia [18]. Alpha-amylase and glucosidase enzymes play a key role in the conversion of complex sugars in to simple glucose that gets absorbed into the blood. Thus, these enzymes are responsible for increasing the blood sugar level. Under diabetic condition, the sugar level was not controlled by insulin, and thus, the blood sugar level stays high (hyperglycemia) for a prolonged period of time leading to cell damage in specific tissues

[16 - 21]. Therefore, inhibition of α -amylase and α -glucosidase enzymes is of great importance in diabetic patients that will directly control the blood sugar level. In our study the protein-ligand docking analysis showed that GW has high affinity towards α -glucosidase and α -amylase enzymes. This suggests that the observed inhibitory activity of GW over α -glucosidase and α -amylase is due to its interaction with these enzymes.

The ethyl acetate (EA) extract (500 $\mu\text{g/ml}$) of *Streptomyces* sp.VITPK9 showed significant (69%) inhibitory activity against α -amylase [22]. The EA extract (500 $\mu\text{g/ml}$) from *Streptomyces* sp.VITSTK7 inhibited α -glucosidase activity by 64% [20]. *Streptomyces corchorusii* has been reported to possess amylase inhibition activity [24]. *Rhodomarinus*, the sub sp. of *Streptomyces corchorusii* showed α -amylase inhibitor activity [23]. Antioxidant and antidiabetic activity of *Streptomyces* sp. VITMSS05 was reported by Revathy *et al.*, 2013 [24]. Significant antioxidant activity of the ethyl acetate extract of *Streptomyces* sp. VITMSS05 was observed with an IC_{50} value of 92 $\mu\text{g mL}^{-1}$. The extract showed 64% inhibition on α -amylase and 91.5% inhibition on α -glucosidase at 100 $\mu\text{g mL}^{-1}$ with an IC_{50} value of 385 and 43 $\mu\text{g mL}^{-1}$. Endophytic actinomycetes *Streptomyces olivochromogenes* has been reported to possess α -glucosidase inhibiting ability [25].

Several compounds extracted from *Streptomyces* species has been reported to possess significant antidiabetic activity [26, 27]. Bioactive antidiabetic compounds voglibose, acarbose, valienamine, adiposin-1, and trestatin-B were reported from *Streptomyces hygroscopicus-limoneus* [28, 29], *Actinoplanes utahensis* [30], *S. calvus* [31] and *S. dimorphogenes* [32] respectively. Lowering of the post prandial blood glucose level by Voglibose through the inhibition of α -glucosidase in diabetic people has been reported. Voglibose is an oral alpha-glucosidase and alpha-amylase inhibitor, first launched by Bayer in Switzerland in 1989 for the oral treatment of type-2 diabetes mellitus, Acarbose was used as α -glucosidase and α -amylase inhibitor [30]. Potent α -glucosidase activity of aminocyclitol, isolated from the fermentation broth of *Streptomyces hygroscopicus* subspecies *limoneus* has been reported. Pyrostatins A and B, the novel compounds extracted from *Streptomyces* sp. has been reported to exhibit specific inhibitory activity against N-acetyl-glucosaminidase (Imada, 2005). The novel antidiabetic compound NFAT-133 extracted from *Streptomyces* strain PM0324667 was reported to induce glucose uptake in L6 skeletal muscle cells [33]. NIFTA has been reported to be effectively reduced systemic glucose levels in diabetic animals.

GW prevents 30% of haemoglobin glycosylation suggests that it is effective in preventing the interaction of glucose with RBCs in blood and it is one of the essential feature of any antidiabetic agent. Increased haemoglobin-glucose level is a serious problem in diabetic patients (hyperglycemia). Glucose forms a covalent bond with haemoglobin, resulting in increased blood plasma sugar level causes damage to insulin-independent organs like kidney, blood vessels, eye lense, *etc.*, Preventing the increase of haemoglobin-glucose level greatly reduces the risk of developing hyperglycemia associated damage. Non-enzymatic glycosylation of haemoglobin is an oxidation reaction and an antioxidant can counter this reaction, thereby preventing the process of glycosylation. Since GW demonstrated significant antioxidant potential, it can prevent haemoglobin glycosylation as well [15, 21].

Glucose uptake assay by yeast cells showed 64% increase in glucose uptake when treated with GW. Increased uptake in yeast cells will occur only when intracellular glucose level is reduced. GW treatment effectively reduces glucose concentration in the yeast cells, thereby causing the cells to take up increased concentrations of glucose [15].

CONCLUSION

GW exhibits antidiabetic activity by inhibiting α -glucosidase and α -amylase enzymes, and prevents haemoglobin glycosylation. It also exhibits free radical scavenging antioxidant activity. The antidiabetic and antioxidant potential of GW can be explored further to develop as an effective antidiabetic agent.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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