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COMBINATIONS OF *Hibiscus sabdariffa* WITH *Zingiber officinale* AND *Allium sativum* INHIBIT α-AMYLASE AND α-GLUCOSIDASE: A GUIDE TO DOCKING OF *H. sabdariffa* CONSTITUENTS

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ABSTRACT

Conventional enzyme inhibitors such as acarbose are widely used for the control of postprandial hyperglycemia by virtue of their inhibitory action on carbohydrate-hydrolyzing enzymes, but are often associated with side effects, necessitating the development of safer plant-derived alternatives. In this study, the in vitro and in silico inhibitory activities of aqueous *Hibiscus sabdariffa* calyx, *Zingiber officinale*, and *Allium sativum* extracts against α-amylase and α-glucosidase were investigated. *H. sabdariffa* (HS) *calyces, Z. officinale* (ZO) roots and *Allium sativum* (AS) bulbs were extracted using an aqueous method. For α-glucosidase inhibition, IC_{50} values were 39.08 µg/mL (HS), 308.91 µg/mL (ZO), 657.64 µg/mL (AS), 139.99 µg/mL (HS + AS), 73.46 µg/mL (HS + ZO), and 21.94 µg/mL (acarbose). Against α-amylase, values were 70.81 µg/mL (HS), 396.43 µg/mL (ZO), 2483.28 µg/mL (AS), 92.04 µg/mL (HS + AS), 79.76 µg/mL (HS + ZO), and 56.14 µg/mL (acarbose). In silico XP docking, acarbose had higher docking scores (-10.699 kcal/mol for α-glucosidase and -13.09 kcal/mol for α -amylase) than 3-hydroxystigmast-5-en-7-one, a HS bioactive compound which showed higher docking scores (-7.463 kcal/mol for α-glucosidase and -4.795 kcal/mol for α -amylase) compared to other HS compounds, justifying the *in vitro* results that revealed acarbose as the most potent inhibitor based on IC_{50}. Although the extracts were less potent than the reference drug acarbose, their natural origin and observed synergistic action are pointers to their prospect as safer controls for postprandial hyperglycemia. Further research elucidating active compounds of HS and validating in vivo antidiabetic activity of this combined extract is recommended.

Keywords: α -amylase, α-glucosidase, Acarbose, *H. sabdariffa, Z. officinale*, *A. sativum*

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that is defined by hyperglycemia caused by derangements in insulin secretion, action, or both (Banday *et al.* 2020). Type 2 diabetes mellitus (T2DM) is the most common type of DM and is strongly linked to dietary imbalance, physical inactivity, and being overweight (Dirir *et al*., 2021). Enzymatic inhibition of the carbohydrate-metabolizing enzymes α-amylase and α-glucosidase is one of the effective therapies for controlling high blood sugar after meals, a state known as postprandial hyperglycemia in T2DM (Li *et al.,* 2022). These enzymes catalyze hydrolysis of complex foodstuffs carbohydrate to the bioavailable simple carbohydrates (Rangel-Galván *et al*., 2024). Whereas clinical efficacy is achieved with synthetic inhibitors such as acarbose, their therapeutic use is sometimes restricted by gastrointestinal side effects such as flatulence, abdominal pain, and diarrhea (Yousefi *et al*., 2023). Considering the above drawback, attempts were made to look for safer inhibitors of these enzymes from plants (Jiang *et al.,* 2019; Wang *et al.,* 2018).

Medicinal plants have a synergistic combination of bioactive phytochemicals with good antioxidant as well as antidiabetic activity. *Hibiscus sabdariffa* or roselle has also been researched in the same vein on its anthocyanins, flavonoids, and phenolic acids, which have been shown to have potent antihyperglycemic and antioxidant activities (Jamrozik *et al*., 2022). Meanwhile, *Zingiber officinale* (ginger) has gingerols and shogaols, and *Allium sativum* (garlic) has organosulfur compounds such as allicin. Such metabolites have been reported to inhibit α-amylase and α-glucosidase activity *in vitro* and enhance glucose metabolism (Rangel-Galván *et al*., 2024).

Combination therapeutics of plant extracts have been shown as a potentiality by complementary interactions of the phytochemical constituents. Polyherbal preparation has also attracted interest as potential worthy alternatives for one plant therapy with increased efficacy and reduced side effects (Jain *et al.*, 2025). Besides, in silico molecular docking provides valuable information on the binding modes of bioactive compounds to the active sites of the enzyme, complementing experimental assays, and assisting identification of active inhibitory compounds (Akanbi *et al*., 2023).

Thus, the present study investigates the *in vitro* inhibitory action of aqueous extracts of calyx of *Hibiscus sabdariffa* (*H. sabdariffa*), roots of *Zingiber officinale* (*Z. officinale*), and bulbs of *Allium sativum* (*Allium sativum*), both individual and combination, on α-amylase and α-glucosidase activity. *In silico* molecular docking was also performed to identify potential bioactive compounds that can inhibit enzymes. The current study attempts to elucidate the antihyperglycemic activity of these plant extracts, emphasizing the synergistic effect of their combination, and also explore possible phytochemical-enzyme interactions that could be a source of information for designing safer and more effective alternatives to conventional antidiabetic drugs.

This study was designed on the basis that the synergistic effect of *Hibiscus sabdariffa*, *Zingiber officinale*, and *Allium sativum* aqueous extracts might result in a stronger inhibition of α-amylase and α-glucosidase activities compared to the lone aqueous extract of each plant. It was therefore, hypothesized that the plants might act synergistically in order to provide stronger interactions with α-amylase and α-glucosidase as a therapeutic strategy for diabetes.

MATERIALS AND METHODS

Collection of Sample and Reagents

Plant materials of *Hibiscus sabdariffa* calyx, rhizome of *Zingiber officinale* and *Allium sativum* were obtained from Oja-tuntun Market in Ilorin, Kwara State (latitude 8.49664 and longitude 4.54214). The plants studied were authenticated and identified by Mr. Bolu Ajayi, a Botanist at the Herbarium, Department of Plant biology, University of Ilorin and were given voucher numbers UILH/001/1589/2023 (*Hibiscus sabdariffa*), UILH/002/1590/2023 (*Zingiber officinale*) and UILH/003/1591/2023 (*Allium sativm*). Dimethyl Sulphoxide (DMSO), potassium phosphate, *p*-nitrophenyl-α-D-glucopyranoside, sodium phosphate, sodium chloride and dinitrosalicyclic acid (DNSA) were all products of Sigma-Aldrich (St. Louis, MO, USA).

Preparation and Reconstitution of Extracts

The *H. sabdariffa* calyces, *Z. officinale* roots and *A. sativum* bulbs were air-dried, and ground separately into fine powder. Thereafter, 1000 g of finely ground powder of each plant materials were used for extraction. Extraction of plant sample was done using the aqueous extraction method. The samples were boiled for 20 minutes, and then sieved. The liquid extracts were lyophilized to obtain the crude extracts. Each sample was reconstituted by dissolution of 5 g of the sample in 1ml of DMSO and 49 ml of methanol. For the *H. sabdariffa* and *Z. officinale* combination, 2.5 g of each sample was weighed (1:1) and mixed together to obtain 5 g of *H. sabdariffa* and *Z. officinale* combined extract. Similar proportion was used to prepare *H. sabdariffa* and *Allium sativum* combined extract. These mixtures were also dissolved in 1ml of DMSO and 49 ml of methanol.

In vitro Analysis

α-Glucosidase Inhibition Analysis

The α-glucosidase assay was performed using the method described by Apostolidis *et al.* (2006). Aqueous extract of *H. sabdariffa, Z. officinale* and *A. sativum* and the combined extracts (500 µl) and 1000 µl of 0.1 M potassium phosphate buffer (pH 6.9) containing α-glucosidase solution (1.0 U/ml) was incubated in water bath at 25 °C for 10 minutes. After 10 minutes of incubation, 500 µl of 5 mM *p*-nitrophenyl-α-D-glucopyranoside solution in 0.1 M potassium phosphate buffer (pH 6.9) was added to each tube at 5 minutes' interval. The reaction mixture was incubated at 25 °C for 5 minutes prior to the reading of absorbance at 405 nm.

α-Amylase Inhibition Analysis

The α-amylase inhibition assay was adapted from Apostolidis *et al*., (2006). Concisely, 250 µl of the *H. sabdariffa, Z. officinale* and *A. sativum* extracts, 500 µl of 0.02 M sodium phosphate buffer, pH 6.9 with 0.006 M sodium chloride containing 0.5 mg/ml a-amylase solution were pre-incubated at 25 ºC for 10 minutes. This was followed by the addition of 500 µl of a 1% starch solution in 0.02 M sodium phosphate buffer, pH 6.9 with 0.006 M sodium chloride to each tube at pre-determined time intervals. The reaction mixtures were incubated at 25 ºC for 10 minutes. The reaction was stopped with 1.0 ml of dinitrosalicyclic acid (DNSA) colour reagent. The test tubes were incubated in a boiling water bath for 7 minutes, afterwards, 1.0 ml of 18.2% potassium tartrate solution was added to each tube after the boiling prior to cooling to room temperature. The reaction mixture was then diluted by adding 10 ml of distilled water and the absorbance was read at 540 nm. Acarbose was used as blank. The readings were compared to a control which had 500 µl of buffer solution instead of the extract. The enzyme inhibition was calculated using the equation below:

$$\% \text{ inhibition} = \frac{Absorbance\ of\ control - Absorbance\ of\ extracts}{Absorbance\ of\ control} \times 100$$

In silico Analysis

Ligand Generation and Preparation

The SDF format of 3D conformers of the 17 bioactive compounds of *H. sabdariffa* reported by Sehim *et al.* (2023) and acarbose, the standard inhibitor of α-amylase and α-glucosidase, were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/compound/), a chemical database managed by the National Center for Biotechnology Information (NCBI) (Adelusi *et al*., 2023). This was done by pasting the name of each compound in the search box of the Pubchem server, clicking on the compound of interest from the lists of compounds in the results, and downloading the SDF format of the compound. These conformers were subsequently prepared using OPLS4 force field at pH 7.00±2.00 for further analysis using the LigPrep feature available in Maestro 13.9.

Protein Preparation

The co-crystallized structures of α-amylase and α-glucosidase were downloaded from the Protein Data Bank (https://www.rcsb.org/). This was done by searching for each of the enzymes on the database, choosing human species and downloading the FASTA format of the enzymes having no mutation (PDB ID: 12BY for α-amylase and 5NN5 for α-glucosidase). To refine the protein structure, the protein preparation wizard from Maestro v13.9 software was employed. The process involved assigning bond orders, deleting waters beyond hets: 5.00, filling the missing loops (using Prime), addressing missing side chains, incorporating hydrogen atoms, optimizing the protein structure at pH 7.4±2.00 with PROPKA, minimizing the protein structure, and minimizing of atomic position with OPLS4 force field.

Receptor Preparation and Molecular Docking

For each protein, a receptor grid generation tool was used to create a grid around the binding site of the prepared protein, highlighting the areas where ligand-protein interactions occur (Alshehri *et al*., 2023). A cubic grid box was automatically generated at the active sites of the enzymes, encompassing all amino acid residues within the binding site housing the co-crystallized ligands. Molecular docking was then performed using Maestro 13.9 with the Glide docking software, employing both standard precision (SP) and extra precision (XP) docking algorithms. The prepared compounds including acarbose (standard inhibitors of the two enzymes) and the protein were docked to predict compounds with the highest binding affinity (kcal/mol). This was carried out making the compounds flexible while the protein was maintained as a rigid body (Alshehri *et al*., 2023).

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 8 (version 8.0.2, GraphPad Software, Inc., La Jolla, CA, USA). All experimental data were obtained from triplicate analyses and were expressed as mean ± standard deviation (SD). Significant differences between the inhibitory activities of the various extracts and their combinations were determined by one-way analysis of variance (ANOVA). To compare the means of different samples at specific concentrations, Tukey's multiple comparisons test was employed as the post-hoc tool. Statistical significance was defined at $p < 0.05$. The half-maximal inhibitory concentration (IC_{50}) values were

calculated by fitting the data to a non-linear regression model (log[inhibitor] vs. normalized response—variable slope) using the software's built-in curve-fitting functionality. The graphical representations of the docking scores were also obtained using scatter plots of the GraphPad Prism.

RESULTS AND DISCUSSION

In this study, aqueous extracts of *Hibiscus sabdariffa* calyx, *Zingiber officinale* roots, and *Allium sativum* bulb were investigated for their inhibitory activities against α-amylase and α-glucosidase. The α-glucosidase inhibitory activity of the single and combined extracts increased proportionally with concentration, exhibiting a clear dose-dependent trend (Figure 1). For α-glucosidase inhibition, IC_{50} values were 39.08 µg/mL for *H. sabdariffa* only, 308.91 µg/mL for *Z. officinale* only, 657.64 µg/mL for *A. sativum* only, 139.99 µg/mL for combined *H. sabdariffa* and *A. sativum* extract, 73.46 µg/mL for combined *H. sabdariffa* and *Z. officinale* extract, and 21.94 µg/mL for acarbose (Figure 1). The α-glucosidase inhibitory profiles observed in this study reveal that *H. sabdariffa* (HS) possesses the most potent individual inhibitory activity based on the observed IC_{50}, significantly outperforming *Z. officinale*. This agrees with the works of Bule *et al.* (2020) that pointed to the strong ability of Roselle to compete for the active enzyme site due to the high content of organic acids and anthocyanins. It is worth noting that the inhibitory potential was seen to have a pronounced improvement in the combined formulation groups compared to the individual garlic and ginger extracts, suggesting that *H. sabdariffa* calyx, when combined with *Z. officinale* roots and *A. sativum* bulbs, may enhance the inhibitory effects of roots and bulbs. This further supports the observation previously reported on the inhibitory effect of *H. sabdariffa* on α-glucosidase (Zulfiqar *et al.,* 2022).

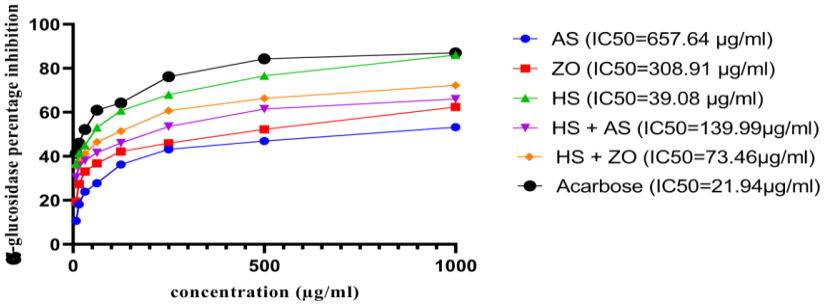


Figure 1: α-Glucosidase inhibitory activity of individual and combined extracts of *Hibiscus sabdariffa* calyces, *Zingiber officinale* roots, and *Allium sativum* bulbs (HS: *Hibiscus sabdariffa*; AS: *Allium sativum*; ZO: *Zingiber officinale*).

Against α-amylase, the IC_{50} values were 70.81 µg/mL for *H. sabdariffa*, 396.43 µg/mL for *Z. officinale*, 2483.28 µg/mL for *Allium sativum*, 92.04 µg/mL for combined *H. sabdariffa* and *A. sativum* extract, 79.76 µg/mL for combined *H. sabdariffa* and *Z. officinale* extract, and 56.14 µg/mL for acarbose (Figure 2). Alpha-amylase inhibitory activity presented in this analysis proves the higher potency of *H. sabdariffa* over *Z. officinale* and *A. sativum*. Such high effectiveness in the HS compound is further ascertained by recent studies, where McCalla & Smith (2024) have underscored the potency in using the high polyphenol content to maintain normal postprandial glucose levels. This α-amylase inhibition result also supports the enhancement of inhibitory effects of *A. sativum* and *Z. officinale* on the enzyme.

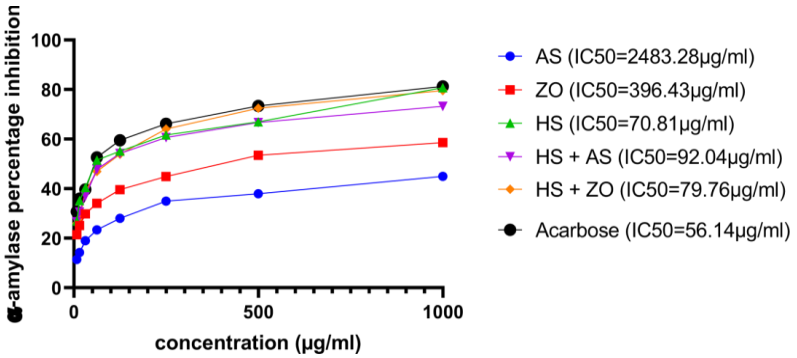
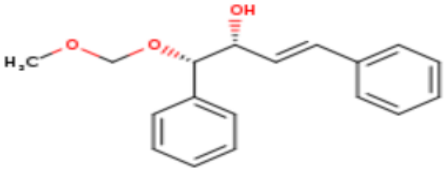
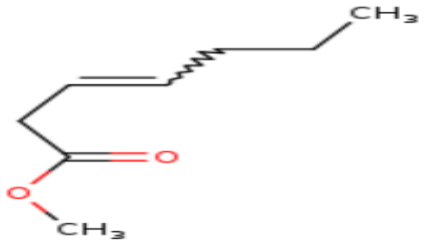
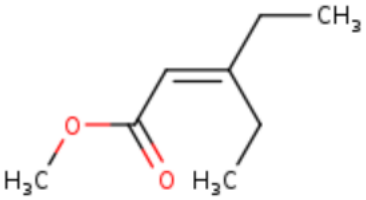
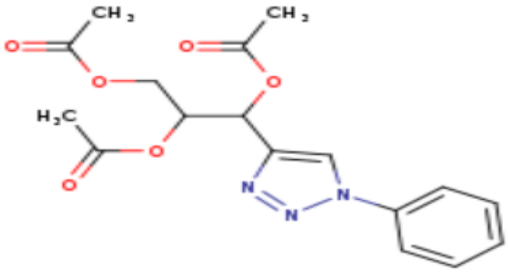
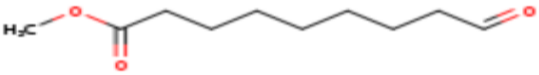
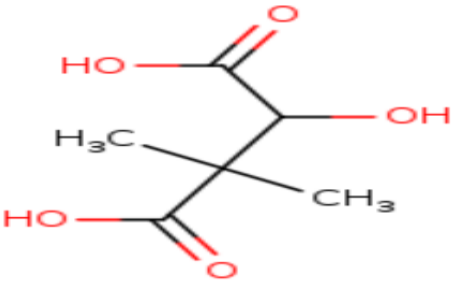
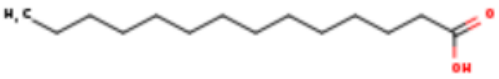
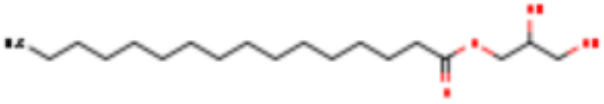
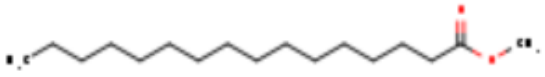
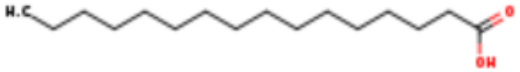
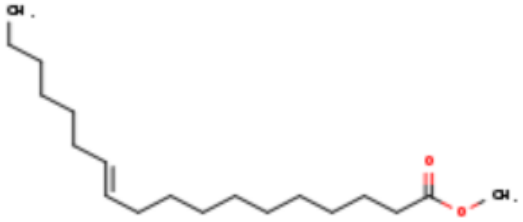
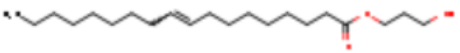
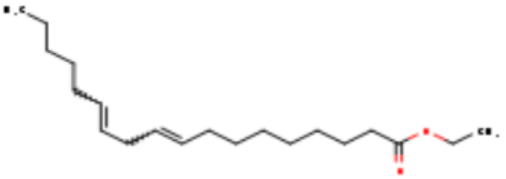
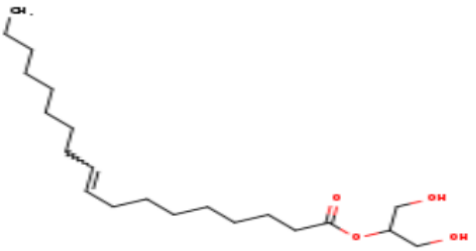
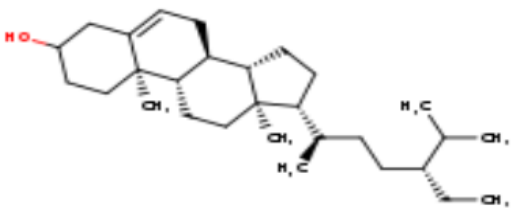


Figure 2: α-Amylase inhibitory activity of individual and combined extracts of *Hibiscus sabdariffa* calyces, *Zingiber officinale* roots, and *Allium sativum* bulbs (HS: *Hibiscus sabdariffa*; AS: *Allium sativum*; ZO: *Zingiber officinale*).

The in silico molecular docking of *Hibiscus sabdariffa* bioactive constituents against α-amylase and α-glucosidase (Tables 1) provided further insights into their interaction mechanisms. The compounds identified included fatty acids, esters, and sterol derivatives such as 3-hydroxystigmast-5-en-7-one, linoleic acid ethyl ester, and 2,3-dihydroxypropyl hexadecanoate.

Table 1: *H. sabdariffa* Bioactive Compounds

S/N	Compounds	Structures
1	1,4-Diphenylbut-3-ene-2-ol	
2	3-Heptenoic acid, methyl ester	
3	2-Pentenoic acid, 3-ethyl-, methyl ester	
4	1,2,3- Propanetriol, triacetate	
5	Nonanoic acid, 9-oxo-, methyl ester	
6	Butanedioic acid,1-hydroxy-2,2-dimethyl-(R)-	
7	Oleic acid	
8	Tetradecanoic acid	

S/N	Compounds	Structures
9	Hexadecanoic acid, 2,3-dihydroxypropyl ester	
10	Hexadecanoic acid, methyl ester	
11	n-Hexadecanoic acid	
12	11-Octadecenoic acid, methyl ester	
13	cis-13-Octadecenoic acid	
14	Oleic acid, 3-hydroxypropyl ester	
15	Linoleic acid ethyl ester	
16	9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester	
17	Stigmast-5-en-3-ol, (3a)-	

Docking analyses using the Standard Precision (SP) and Extra Precision (XP) modes showed that acarbose consistently displayed the strongest binding affinity for both enzymes. For α-amylase, SP docking scores were -6.601 for acarbose, -3.531 for 2,3-dihydroxypropyl hexadecanoate, -6.219 for 3-hydroxystigmast-5-en-7-one, -3.324 for methyl 3-ethyl pent-2-enoate, and -3.339 for 3-hydroxypropyl oleate (Figure 3). In XP mode, the corresponding scores were -13.09, -4.961, -4.795, -3.247, and -2.598, respectively (Figure 4).

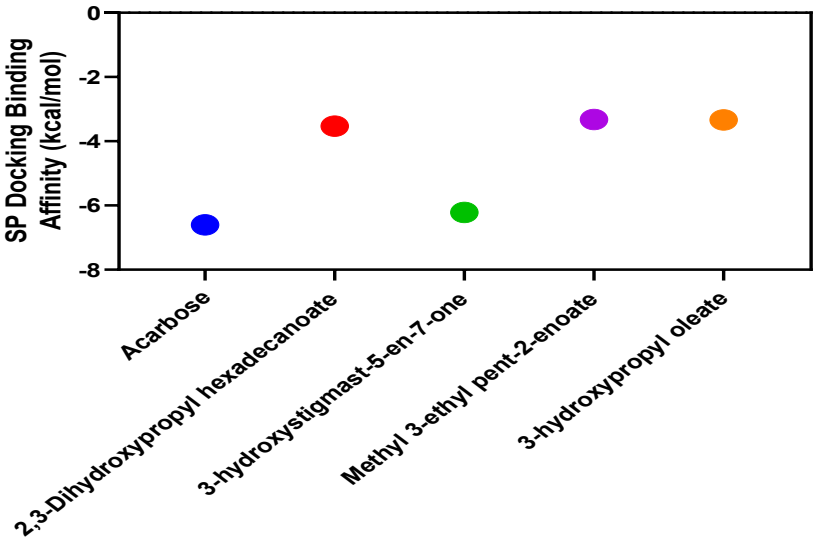


Figure 3: Standard Precision Docking Binding Affinity of *Hibiscus sabdariffa* Extract on α-Amylase

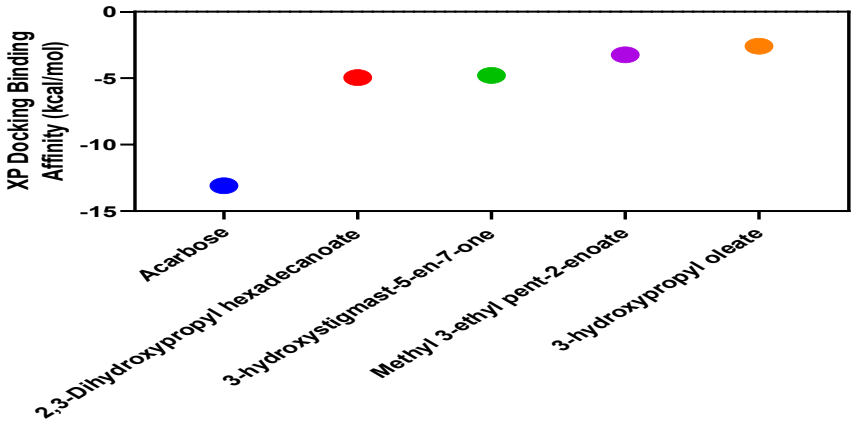


Figure 4: Extra Precision Docking Binding Affinity of *Hibiscus sabdariffa* Extract on α-Amylase

For α-glucosidase, SP docking scores were -6.055 for acarbose, -6.08 for 3-hydroxystigmast-5-en-7-one, and -3.283 for methyl 3-ethyl pent-2-enoate (Figure 5), while in XP mode, the scores were -10.699, -7.463, and -2.914, respectively (Figure 6). These results indicate that 3-hydroxystigmast-5-en-7-one exhibits strong binding affinity toward both enzymes, closely approaching that of acarbose, suggesting its potential as a natural inhibitory compound. The findings of this study align with earlier reports that phenolic, flavonoid, and anthocyanin-rich plants possess α-amylase and α-glucosidase inhibitory activity through competitive or noncompetitive mechanisms, while also exerting antioxidant and anti-inflammatory effects (Jomova *et al*., 2025). The enhanced inhibitory performance of the combined extracts may be attributed to synergistic interactions among diverse phytochemicals such as phenolics, terpenoids, sterols, and sulfur-containing compounds. These bioactive compounds may act at different enzyme sites or modulate oxidative stress pathways, thereby collectively improving enzyme inhibition efficiency (Jain *et al*., 2025).

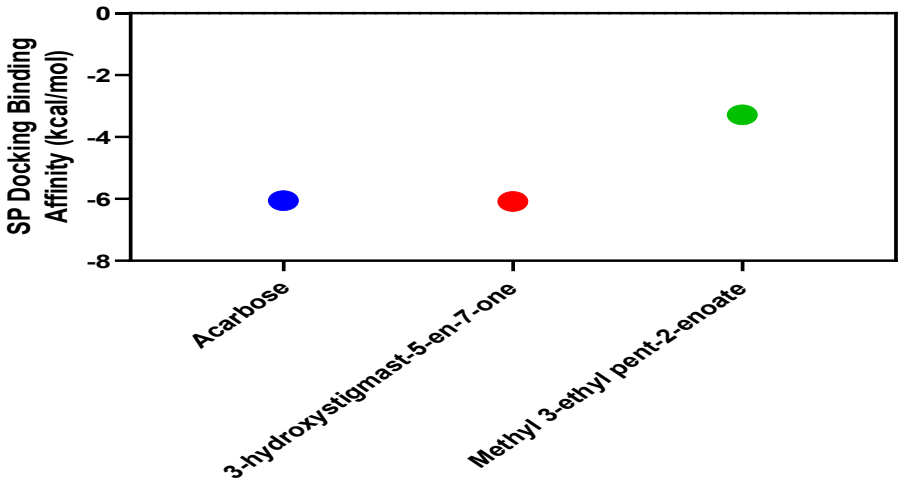


Figure 5: Standard Precision Docking Binding Affinity of *Hibiscus sabdariffa* Extract on α-Glucosidase

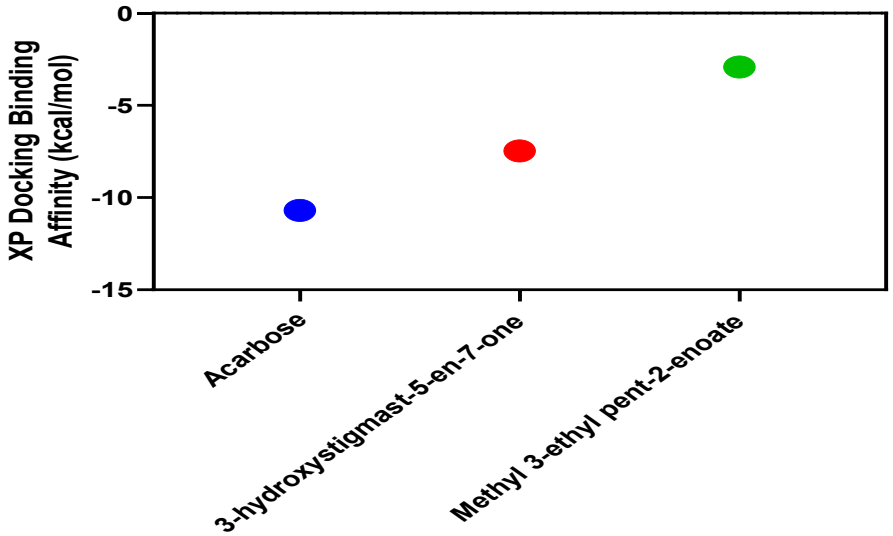


Figure 6: Extra Precision Docking Binding Affinity of *Hibiscus sabdariffa* Extract on α-Glucosidase

The docking results support the in vitro findings, as sterol derivatives like 3-hydroxystigmast-5-en-7-one showed favorable binding at the enzyme active sites, consistent with prior computational studies of natural inhibitors of α-amylase and α-glucosidase (Ayorinde *et al*., 2023). Nevertheless, none of the identified compounds matched the inhibitory strength of acarbose, reaffirming its higher potency but also highlighting the importance of these plant-derived compounds as safer, natural alternatives. Generally, the study demonstrates that aqueous extracts of *Hibiscus sabdariffa*, *Zingiber officinale*, and *Allium sativum* inhibit α-amylase and α-glucosidase activities in concentration-dependent manners, with the combined extracts exhibiting synergistic effects and enhanced inhibition. These results support their potential use as complementary natural agents in diabetes management.

The bioactive compounds with high binding affinity and the standard inhibitor formed hydrogen bonds with different amino acid residues of the two enzymes (Figures 7 and 8), suggesting the ability of the ligands to bind to the enzymes. The standard inhibitor of the two enzymes, acarbose had higher hydrogen bonds with the two enzymes compared to the test compounds. However, acarbose violates the Lipinski's rule of five due to a molecular weight greater than 500 Da, more than 10 hydrogen bond (HB) acceptors (N or O), and more than 5 hydrogen bond donors (NH or OH) (Akinyede *et al.,* 2021). The 2,3-dihydroxypropyl hexadecanoate with 5 HBs showed higher interaction with α-amylase compared to other docked bioactive compounds.

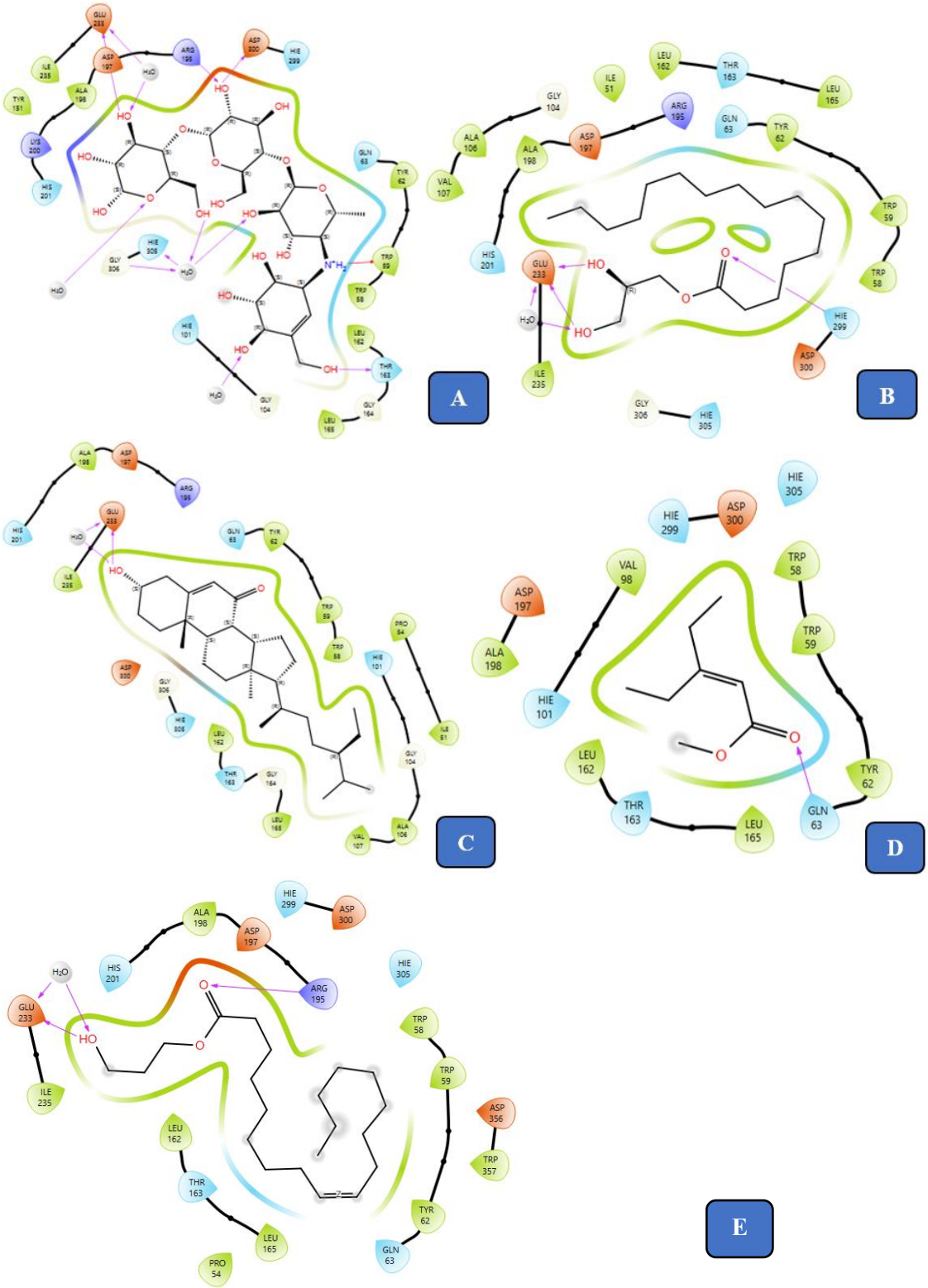


Figure 7: XP docking 2D interaction of α-Amylase with (a) Acarbose (b) 2,3-dihydroxypropyl hexadecanoate (c) 3-hydroxystigmast-5-en-7-one (d) methyl 3-ethyl pent-2-enoate (e) 3-Hydroxypropyl oleate.

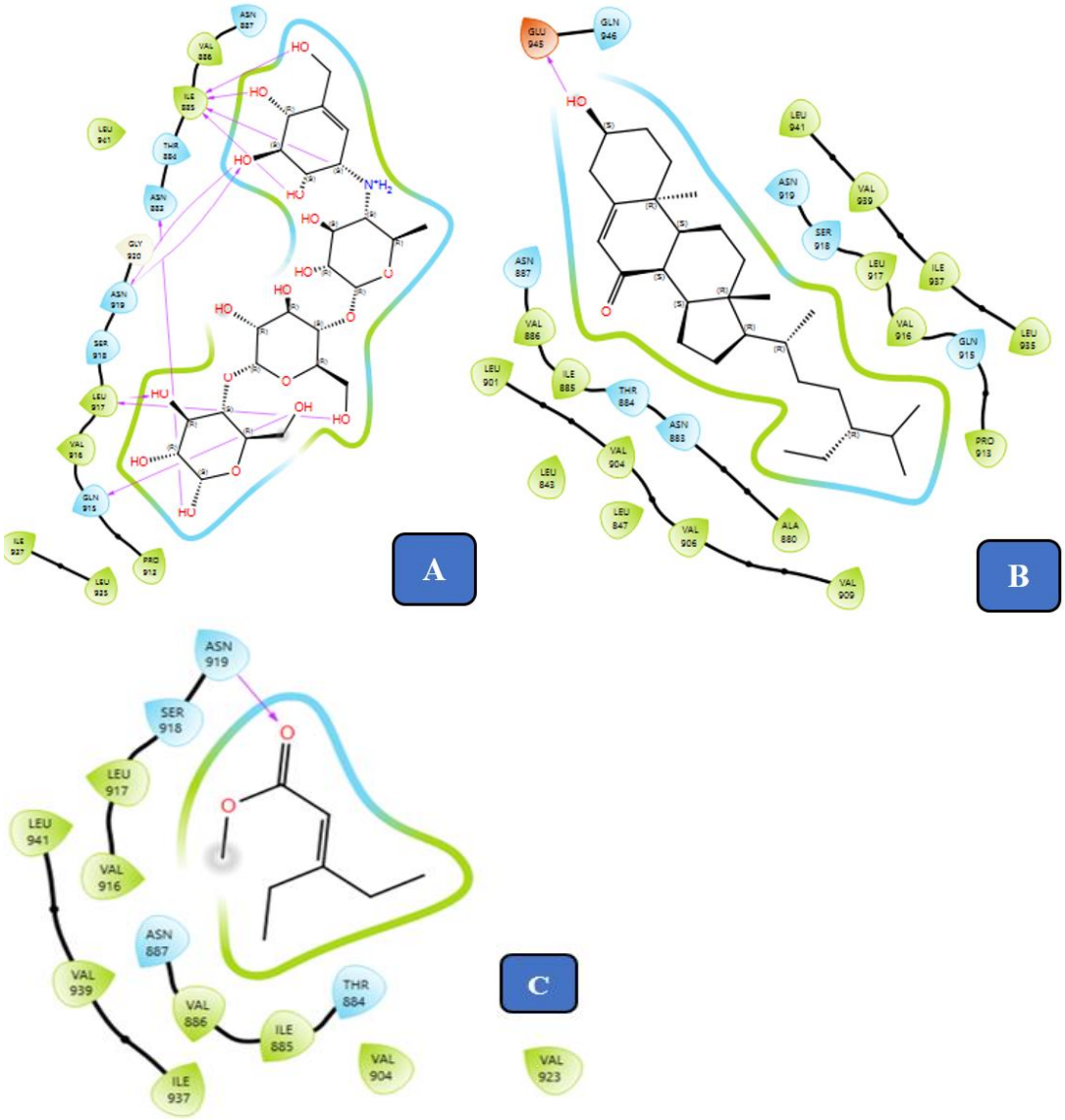


Figure 8: XP docking 2D interaction of α-Glucosidase with (a) Acarbose (b) 3-hydroxystigmast-5-en-7-one (c) methyl 3-ethyl pent-2-enoate

CONCLUSION

The study proved aqueous extracts of *Hibiscus sabdariffa* calyx, *Zingiber officinale* rhizome, and *Allium sativum* bulb are able to inhibit α-amylase and α-glucosidase activities in concentration-dependent manners. The effects of combined extracts were more intense than individual ones, indicating a potential synergistic effect. Molecular docking showed some phytochemicals, particularly 3-hydroxystigmast-5-en-7-one, interact with the enzymes in a beneficial manner, corroborating the experiments. While the activity of these compounds was less than that of acarbose, they potentially provide more naturally safe alternatives for diabetes therapy.

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