

Original Research Article

Determination of Antioxidant and α -Amylase Inhibition Properties of Alligator Pepper (*Aframomum Melegueta*): A Potential Therapeutic Against Diabetes Mellitus

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Abstract: Diabetes is a chronic metabolic disease characterized by raised levels of blood glucose, which over time leads to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. α -amylase Plays a major role in the digestion of starch and glycogen. Thus, inhibitors of this enzyme delay the breakdown of carbohydrates in the small intestine, thereby diminishing postprandial blood glucose in the diabetic patient. In this study, a DPPH radical scavenging activity and computational approaches were employed to uncover the potential of *Aframomum Melegueta* phytochemicals against type two diabetes mellitus mainly by molecular docking, molecular dynamic simulation, MMPBSA and ADMET analysis. The results show that it has high antioxidant properties. Molecular docking indicates that laurifolin, genkwanin and galunolactone have good binding scores of -9.9 kcal/mol, -8.9 kcal/mol and -8.2 kcal/mol, respectively. And have interacted with at least two of the catalytic triads of α -amylase; Asp 300, Glu 233 and Asp 197. Molecular dynamic simulation results show that all the compounds are stable at the active site of the enzyme. Furthermore, MMPBSA analysis revealed they bind strongly with the binding energy of -21.77 ± 1.03 Kcal/mol, -17.82 ± 0.84 Kcal/mol and 15.07 ± 0.26 Kcal/mol for laurifolin, genkwanin and galanolactone. ADMET analysis indicated that all the ligands are water-soluble, drug-like and safe. This study shows that *A. Melegueta* extract has antioxidant properties and possess phytochemicals that can be exploited for further anti-diabetic drug development.

Keywords: Diabetes mellitus, α -amylase, *Aframomum Melegueta*, phytochemicals, Molecular docking, drugs discovery, molecular dynamic simulations and MMPBSA.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose level. Type2 accounts for Over 90% of DM cases, resulting from defective insulin secretion by pancreatic cells and the inability of insulin-sensitive tissues to respond to insulin. Progression of the disease disrupts glucose homeostasis, which gives rise to hyperglycemia. The chronic metabolic imbalance associated with this disease puts patients at high risk for long-term macro and microvascular complications, leading to cardiovascular diseases (Leahy, 2005). In 2019, diabetes was responsible for 4.2 million deaths and 463 million adults were living with the disease, which is

expected to reach 700 million by 2045 (International Diabetes Federation (IDF)). Proper glycemic control remains the main basis for managing T2DM (Zimmet, Alberti, & Shaw, 2001). α -amylase secreted by salivary glands and pancreas plays a major role in the digestion of starch and glycogen. Thus, inhibitors of α -amylase delay the breakdown of carbohydrates in the small intestine, thereby diminishing postprandial blood glucose in T2D (Oyedemi *et al.*, 2017). Carbohydrate hydrolyzing enzyme inhibitors used in the clinical treatment of type 2 diabetes include acarbose, miglitol and voglibose. These inhibitors have side effects such as flatulence, diarrhea and liver disorder (Derosa & Maffioli, 2012). More recently, natural products have attracted scientists' attention and interest. Oxidative

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stress has been demonstrated in many studies to play a significant role in diabetes mellitus (DM) pathogenesis. Antioxidants have already been shown to be prospective in the treatment of diabetes (Oyedemi *et al.*, 2017). Alligator Pepper (also known as mbongo spice or hepper pepper) is a West African spice made from the seeds and seed pods of *Aframomum danielli*; its seeds have been reportedly used in folkloric medicine in the management of hypercholesterolemia, anti-diabetes and hypertension with the limited scientific basis for their action (Kazeem, Akanji, Hafizur, & Choudhary, 2012).

As such, this study aims to determine the antioxidant properties of alligator pepper (*A. Melegueta*) extract and the *in silico* identification of α -amylase inhibitors with the potential to be used in the development of anti-diabetic drugs.

EXPERIMENTAL SECTION

Sample Collection and Extraction

A. Melegueta was collected from Wudil and identified at the Biology Department of Kano University of Science and Technology, Wudil. Methanolic extracts were prepared using 25g of grounded sample soaked in 100 mL of methanol solvent and shaken continuously for 7 d at 25°C in a shaker. The extracts were then filtered using Whatman No. 1 filter paper and allowed to evaporate at room temperature (Haruna, Abdulmumin, Abdulmumin, Murtala, & Dalhatu; Murtala *et al.*).

Determination of Antioxidant Activity of Alligator Pepper

The antioxidant activity was estimated using DPPH (2,2-Diphenyl-1-Picryl-Hydrazyl-Hydrate) free radical scavenging assay was conducted according to the standard procedure. 2ml of various concentrations (0.2-1.0ml) of the plant extract was added separately to 2ml of 0.1mmol/L methanolic solution of DPPH and incubated for 30 minutes in the dark at room temperature in triplicate (Murtala *et al.*). The absorbance was measured against a control 517nm. The scavenging rate (1%) on the DPPH radical was calculated using the expressions.

$$\text{DPPH radical Scavenging rate} = \frac{\text{Absorbance of Control} - \text{Absorbance of Sample}}{\text{Absorbance of Control}} \times 100$$

The concentration with 50% inhibition (IC50) was determined from the calibration curve.

GC-MS Analysis

The bioactive compounds extracted from *A. melegueta* were analyzed by gas chromatography (GC-MS, Shimadzu, Japan) coupled with a mass spectrometer (Shimadzu, Kyoto, Japan) according to the standard protocol. The names, structures, and molecular weights of the bioactive components in each extract were determined by matching their mass spectra with

available data from the NIST and Wiley libraries (Mariswamy, Gnanaraj, Antonisamy, Adaikalam, & Jamesraj, 2013).

Molecular docking

Three-dimensional structures of the identified phytochemicals were retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov). The PDB structure of alpha-amylase (PDB ID: 1PIF) was downloaded from the Protein Data Bank (<https://www.rcsb.org>). And prepared using Discovery studio software.

Molecular docking study was performed by Site-directed docking around the alpha-amylase active site residues with all the identified compounds of *A. melegueta* using Pyrx-AutoDock Vina software package. The receptor molecule remains rigid and the ligands are flexible. Binding interactions were analyzed using Discovery Studio visualize (version 20) (Trott & Olson, 2010).

Molecular dynamic simulations

Molecular dynamic (MD) simulations of the protein and protein-ligand complex were performed with a GROMACS 5.0 package using CHARMM 36 force field (Pronk *et al.*, 2013; Vanommeslaeghe *et al.*, 2010). The complexes were solved with a TIP3P water molecule and neutralized with the 0.154 moles/liter NaCl. The initial energy minimization process was conducted by applying a simulated annealing method with a corresponding equilibration of 1 ns. The production of MD simulation was performed for 50 ns per system at a constant temperature and pressure of 300 K and 1 atm, respectively, with a time step of 2 fs. Root mean square deviation (RMSD) and Root mean square fluctuation (RMSF) were calculated to determine the stability of the protein-ligand complex.

Binding free-energy calculations using MMPBSA

The binding free-energies (ΔG_{bind}) of the candidates were computed using the Molecular Mechanics Poisson-Boltzmann Surface Area (MM-PBSA) algorithm. The total binding free-energy (ΔG_{total}) is determined as a total energy released from the ligand-protein complex which is contributed by molecular mechanics binding energy (ΔE_{MM}) and solvation free energy (ΔG_{sol}) using the following equations:

$$\begin{aligned} \Delta E_{\text{MM}} &= \Delta E_{\text{int}} + \Delta E_{\text{ele}} + \Delta E_{\text{vdw}} \\ \Delta G_{\text{sol}} &= \Delta G_{\text{pl}} + \Delta G_{\text{np}} \\ \Delta G_{\text{total}} &= \Delta E_{\text{MM}} + \Delta G_{\text{sol}} \\ \Delta G_{\text{bind}} (\text{MM-PBSA}) &= \Delta E_{\text{MM}} + \Delta G_{\text{sol}} - \Delta T \Delta S \end{aligned}$$

Where ΔE_{int} stands for internal energy, ΔE_{ele} electrostatic energy, ΔE_{vdw} for vander Waals energy, ΔG_{pl} for polar energy, ΔG_{np} for non-polar energy components and ΔG_{sol} is the contribution to total solvation free energy while ΔG_{bind} stands for the free

energy of binding evaluated after entropic calculations $-T\Delta S$ (Miller III *et al.*, 2012).

ADMET analysis

SwissAdme (www.swissadme.ch) server was used to evaluate the metabolic and toxicological properties of the phytochemicals. The canonical format of the chemical compounds was used as the entry system for ADMET (absorption, distribution, metabolism and toxicity) calculations (Ntie-Kang, 2013).

Data Analysis

The data obtained was analyzed at P-value ($p < 0.05$). Using one way analysis of variance (ANOVA). Data was expressed as the mean \pm Standard deviation. Statistical significance was accepted at a level of $P < 0.05$.

RESULTS

DPPH Radical Scavenging Capacity of Alligator Pepper

A. melegueta extract exhibited a considerable DPPH radical scavenging capacity in a concentration-dependent manner with ascorbic acid used as control (Figure 1).

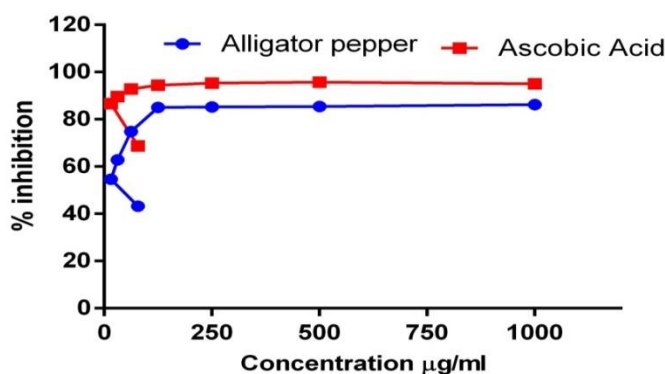


Figure 1: DPPH Radical Scavenging Capacity of Alligator Pepper

Fig 1 illustrates the free radical scavenging activities of Alligator Pepper compared with Ascorbic acid. DPPH value at 1000, 500, 250, 125, 62.5, 31.25, 15.625, 7.8 are 86.24, 85.42, 85.21, 85.0025, 74.85, 62.87, 54.62 and 43.28 respectively. While for ascorbic acid are 95.06, 95.79, 95.31, 94.43, 92.83, 89.64, 86.67, and 68.76 at 100, 500, 250, 125, 62.50, 31.25, 15.62, 7.8, respectively. The IC50 of *A. melegueta* was found to be 0.393 mg/ml.

Molecular Docking

The result shows that *A. melegueta* has phytochemicals that can interact with the catalytic residues of α -amylase (Figure 2). Laurifolin has the highest binding scores of -9.9 kcal/mol followed by Genkwanin with the binding scores of -8.9 kcal/mol and galanolactone with binding scores of - 8.2 kcal/mol (Table 1).

Table 1: Binding scores and interactions between *A. melegueta* phytochemicals and α -amylase

Compound	PubChem ID	Binding Scores (kcal/mol)	Hydrogen Bond	Other interactions
Laurifolin	44257868	-9.9	Gln 63	Glu 233, Asp300, His 305 and Asp 197
Genkwanin	5281617	-8.9	Gln 63	Glu233,Asp17,His 299 and Tyr 58
Galanolactone	146156530	-8.2	-	Asp 300,Asp197,lu 233,Arg195 and His 305

Analysis of the phytochemicals interactions

Alligator pepper phytochemicals interactions with the α -amylase were explored using discovery studio. As shown in Figure 2a, Laurifolin forms two hydrogen bonds with Glu 63 and hydrophobic interactions with Asp 300, Asp197 and Glu 233

catalytic triad of α -amylase genkwanin also forms hydrogen bonds with Glu 63 and hydrophobic interactions with Glu 233 and Asp 197 of the α -amylase catalytic residues (Figure 1b). Similarly, galanolactone also interacted with the active site Asp 300, Glu 233, Asp193 and His 299 (Figure 2c).

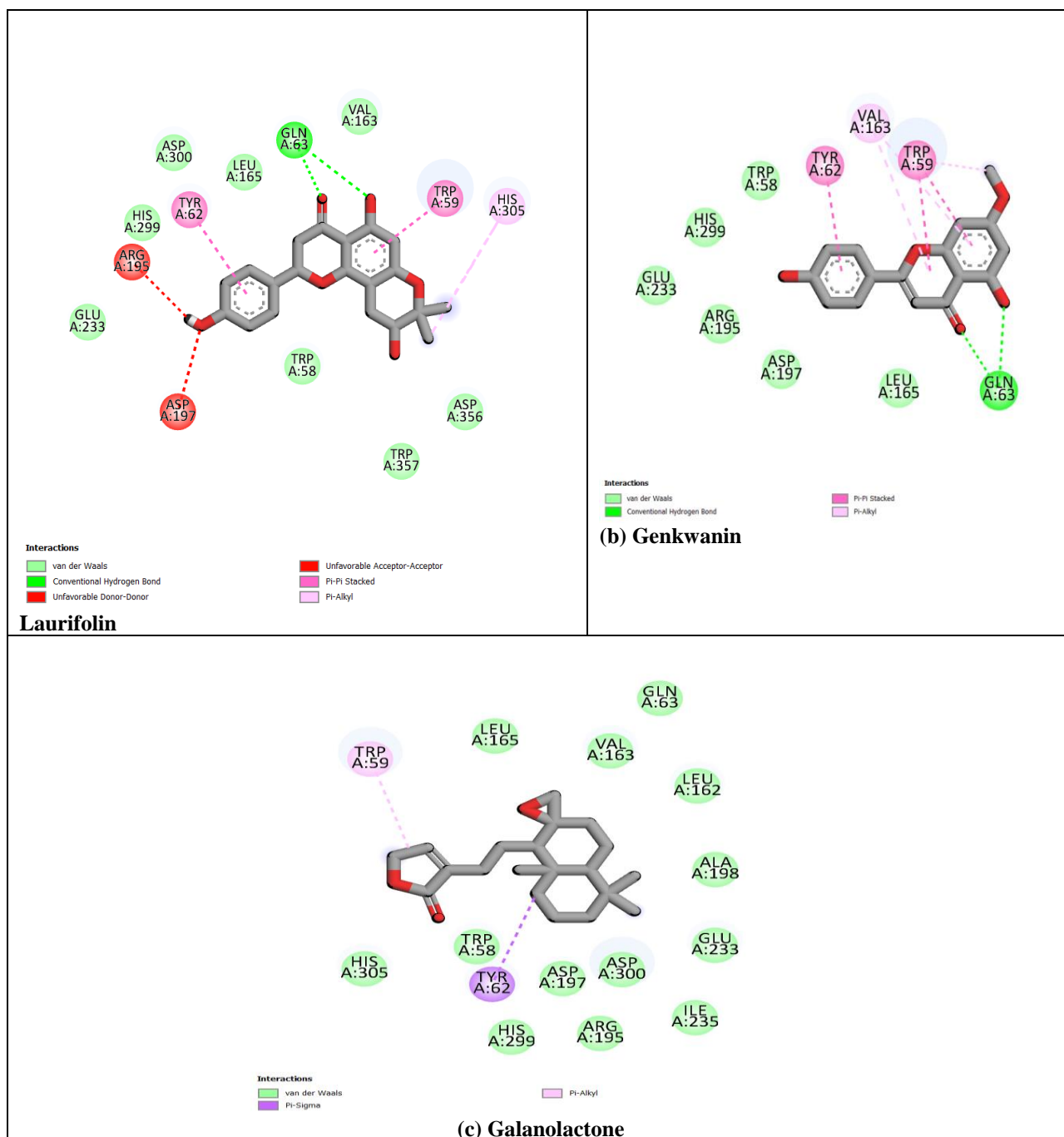


Figure 2: Molecular interactions of the Alligator pepper phytochemicals with the α -amylase

Molecular dynamics (MD) simulation

Dynamic behavior and stability of the protein-ligand complex were determined by MD simulation of 50ns and investigated by RMSD and RMSF analysis.

Root mean square deviation (RMSD)

RMSD results shown in Fig 3 revealed that α -amylase-laurifolin and α -amylase- Genkwanin complexes have RMSD values lower than the Apo-protein, indicating an increase in the stability of the complexes, which remain stable throughout the simulations. On the other hand, α -amylase-

Galanolactone has RMSD values higher than the Apo-protein but remains stable throughout the simulation. Laurifolin RMSD value fluctuates between 0.6Å and 1.2 Å, with the average RMSD value of 0.8 Å. However, genkwanin fluctuates between RMSD values of 0.2 Å and 1.2 Å, with an average RMSD value of 0.8 Å. Similarly, galanolactone RMSD fluctuates between 1.0 Å and 2.0 Å, with the average RMSD value of 1.5 Å. Two major fluctuations observed in the Apo-protein around 10ns to 15ns and 35ns to 40 ns were stabilized upon binding of the ligands.

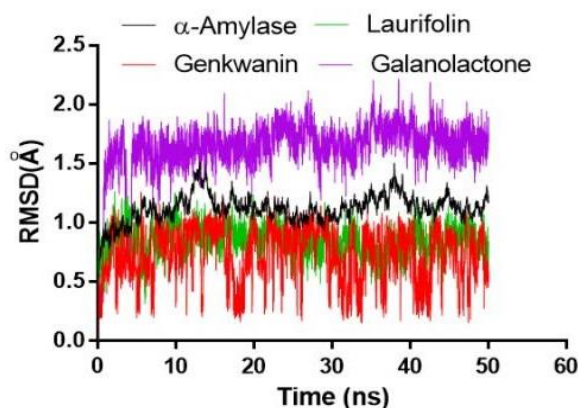


Figure 3: Root mean square deviation (RMSD) of C- α -N backbone for solvated α -amylase in Apo-state and in complex with the ligands over the time of 50 ns simulation

Root mean square fluctuation (RMSF)

RMSF analysis was conducted to determine the residual fluctuations of the system. The result shows that the stability of the enzyme was not significantly affected by the ligands binding, especially around the catalytic residues, Asp 300, Asp197 and Glu 233

(Figure 4). Major fluctuations were observed between residue 235 and 240 (2.19Å) upon binding of laurifolin and between residue 290 and 305 (1.70 Å) upon binding of Galanolactone. Largest fluctuation was observed with Genkwanin at residue between 290 and 305 (3.48Å).

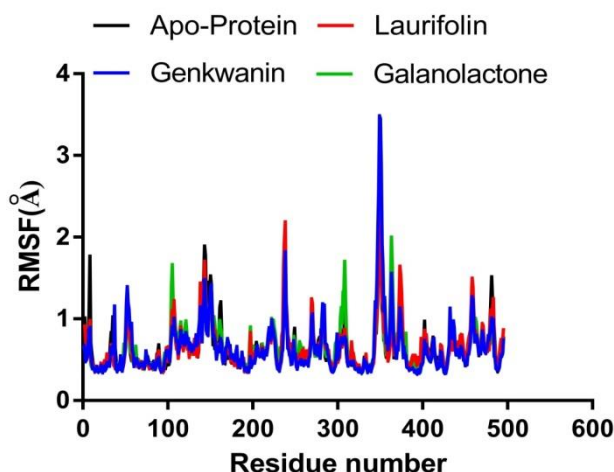


Figure 4: Root mean square fluctuation (RMSF) of α -amylase and in complex with alligator pepper ligands

MMGBSA study

All the 3 ligands were subjected to a ligand-receptor binding energy study using the MMPBSA

approach. The binding energy of the docked ligand complex confirms the stability of the ligand after binding to the enzyme's active site.

Table 2: Binding energy of α -amylase in complex with the ligands using MMPSA

Complex structures	Vander Waals Energy (\pm SD) (Kcal/mol)	Electrostatic Energy (\pm SD) (Kcal/mol)	Polar Solvation Energy(\pm SD) (Kcal/mol)	Apolar Energy (\pm SD) (Kcal/mol)	Total Binding Energy (\pm SD) (Kcal/mol)
α -Amylase-Genkwanin	-28.17 \pm 0.04	-28.15 \pm 0.68	37.39 \pm 0.29	-2.85 \pm 0.02	-21.77 \pm 1.03
α -Amylase-Laurifolin	-37.54 \pm 0.56	-23.95 \pm 1.49	47.34 \pm 0.07	-3.66 \pm 0.02	-17.82 \pm 0.84
α -Amylase-Galanolactone	-26.83 \pm 0.26	-5.17 \pm 1.41	20.09 \pm 1.39	-3.17 \pm 0.02	-15.07 \pm 0.26

The result shows that vander waals interaction mainly drives the binding (Table 2). Genkwanin (-21.77 \pm 1.03 Kcal/mol) has higher total

binding energy compared to laurifolin (-17.82 \pm 0.84 Kcal/mol) and galanolactone (-15.07 \pm 0.26 Kcal/mol). Unfavorable contributions from polar solvation energy

are relatively higher in laurifolin (47.34 ± 0.07 Kcal/mol), followed by genkwanin (37.39 ± 0.29 Kcal/mol) and least in galanolactone (20.09 ± 1.39 Kcal/mol).

Drug-likeness properties and ADMET Screening

ADMET properties of the ligands were analyzed with a Swissadme server. All the compounds have obeyed the Lipinski rule of 5 for drug-likeness (Benet, Hosey, Ursu, & Oprea, 2016); they are found to

be water-soluble and highly absorbed through GIT. Laurifolin has a molecular weight of 356.37g/mol, 6 hydrogen bond acceptors and 3 hydrogen bond donors, while Genkwanin has a molecular weight of 284.26g/mol, 5 hydrogen bond acceptors and 2 hydrogen donors. Galanolactone has a molecular weight of 318.45g/mol, 3 hydrogen bond acceptors and 0 hydrogen donors. Furthermore, they are found to be relatively safe with minimal side effects

Table 3: ADMET Properties of the identified compounds

	Genkwanin	Laurifolin	Galanolactone
Water solubility	Moderately soluble	Moderately soluble	Moderately soluble
Blood-brain barrier permeant	No	No	Yes
Human intestinal absorption	High	High	High
Drugs likeness (Lipinski)	Yes	yes	Yes
Lead likeness	Yes	No	No
P-gp substrate	No	yes	No
CYP1A2 inhibitors	Yes	No	No
CYP2C19 inhibitors	No	No	No
CYP2C9 substrate	yes	No	Yes
CYP2D6 substrate	Yes	yes	No
CYP3A4 inhibitors	yes	yes	No

DISCUSSIONS

α -amylase is an enzyme that is present in pancreatic juice and saliva. It digests carbohydrates and increases the postprandial glucose level in diabetic patients. Inhibiting the activity of the enzyme can control postprandial hypoglycemia (Oyedemi *et al.*, 2017). Several inhibitors of this enzyme with varying efficacy but limited information on their interaction with the enzyme have been reported (Derosa & Maffioli, 2012). In silico molecular docking can provide more insights into understanding their mode of action. Our study revealed that all of the phytochemicals have interacted with the enzyme's active site, highlighting their potential to inhibit α -amylase. They form strong bonds with at least two α -amylase catalytic triads necessary for its catalysis (Pinto *et al.*, 2015). We also found by MM-PBSA studies that they have very high binding energy at the active site; among them, genkwanin (-21.77 ± 1.03 Kcal/mol) tends to bind much stronger, followed by laurifolin (-17.82 ± 0.84 Kcal/mol) and galanolactone (-15.07 ± 0.26 Kcal/mol). ADMET analysis shows that Genkwanin, laurifolin and Galanolactone have obeyed Lipinski rule of 5; water-soluble, highly absorbed through GIT, and not toxic to humans. Furthermore molecular dynamic studies show that the ligands are highly stable at the active site of the enzyme. Antioxidant studies revealed high radical scavenging activity of the *A. melegueta* extract (0.393mg/ml), which is comparable to the findings of Kazeem *et al.*, (IC₅₀ 0.125 mg/mL, using 80% acetone extract) (Kazeem *et al.*, 2012). Numerous studies have revealed the therapeutic potential of genkwanin which is a flavonoid with anti-inflammatory activity, anti-bacterial, anti-plasmodia

and radical scavenging activity (Porras, Bacsa, Tang, & Quave, 2019). laurifolin is a flavonoid which was previously found in *flourensia laurifolia* with broad range of bioactivities such as anti-tumor (Kurkin, Sentsov, Zapesochnaya, Braslavskii, & Tolkachev, 1994). While galanolactone is a di-terpenoid lactone that was reported to have an anti-obesity effect through down-regulating adipogenic transcription factors and adipogenic marker genes (Ahn & Oh, 2012). Our findings and the above clarifications indicated that alligator pepper phytochemicals possess significant broad-spectrum medicinal activities and could be explored further by in-vitro studies to develop new effective drugs against diabetes mellitus.

CONCLUSION

Diabetes mellitus remains among the leading health issues around the globe. One of its therapeutic approaches is by inhibiting the digestion of dietary carbohydrates which α -amylase plays an important role. Based on molecular docking, molecular dynamic simulation, MMPBSA and ADMET analysis, we can conclude that Alligator pepper's laurifolin, genkwanin and galanolactone could strongly bind and inhibit α -amylase activity and thereby control diabetic complications. This study will accelerate the design of new drugs with high clinical value and should be explored further by in-vitro studies to confirm their efficacy.

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Competing Interests: The authors declare no conflict of interest.

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