Clinical Phytoscience

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Molecular interaction of bioactive compounds from *Senecio biafrae* leaf with α-amylase and α-glucosidase receptors

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Abstract

Background: Diabetes mellitus is one of the silent killer diseases affecting millions of people globally and some of the key enzymes in managing this disease are α-amylase and α-glucosidase This study was designed to investigate the possible molecular interactions between various bioactive compounds of *Senecio biafrae* leaf on α-amylase and α-glucosidase (enzymes) receptors an important target protein in Type 2 diabetes mellitus.

Methods: This study involved the investigation of the of gallic acid, chlorogenic, caffeic acid, rutin, quercetin, and kaempferol (ligands) for Lipinski's rule of five using Molinspiration, ADMET profiles using admetSAR server and molecular docking of 3D structures of the six bioactive compounds and metformin against α-amylase and α-glucosidase were carried out using AutoDockVina.

Results: The results revealed that caffeic acid, quercetin, and kaempferol obey Lipinski's rule of five. All the ligands demonstrated high gastrointestinal tract absorption except rutin and chlorogenic acid, only one can serve as a P-glycoprotein substrate and three of the ligands used can act as cytochrome P450 inhibitors isoforms. All the ligands had a high binding affinity than metformin (the standard drug used).

Conclusion: In can be concluded that some of the bioactive compounds (especially caffeic acid) in *Senecio biafrae* leaf have antidiabetic activity, which they may serve as a potential antidiabetic drug in the management of diabetes mellitus than metformin.

Keywords: *Senecio biafrae* leaf, α-Amylase, α-Glucosidase, Receptors, Bioactive compounds

Introduction

Type 2 diabetes mellitus (T2DM) has been known with hyperglycaemia, which can lead to series of health complications like nephropathy, neuropathy, retinopathy, and cardiovascular disease [6]. Alqahtani et al. [7] documented that T2DM is one of the health diseases and accounting for more than 90% incidence of diabetes mellitus globally.

The main therapeutic method of managing postprandial hyperglycaemia in T2DM is by inhibiting the digestion of nutritional carbohydrates [5]. Furthermore, pancreatic α-amylase is the main enzyme involves in breaking down nutritional polysaccharides into disaccharides and by another important enzyme known as α-glucosidases to monosaccharides (e.g. glucose), which can be absorbed into the bloodstream. α-glucosidase is an enzyme found in the brush border of the small intestine epithelium [12]. Hence, inhibiting α-amylase and α-glucosidase enzymes can help in retarding nutritional carbohydrate digestion and glucose uptake [20].

Currently, there are several conventional drugs available in managing T2DM, these include acarbose, voglibose, and miglitol but these are characterized by different side effects [10]. Therefore, it is believed that bioactive compounds from medicinal plants are known with little or no side effects [24], an example of such a

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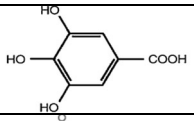
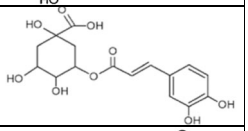
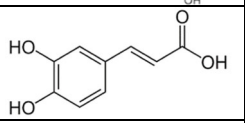
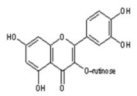
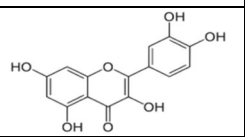
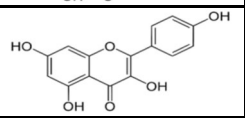
Table 1 Bioactive compounds identified in *Senecio biafrae* leaf

S/No	Compound Name	Chemical Class	Compound PubChem ID	Molecular formular	SMILE	Chemical structure
1	Gallic acid	Phenol	CID 370	$C_7H_6O_5$	C1=C(C=C(C(=C1O)O)O)C(=O)O	
2	Chlorogenic acid	Phenol	CID 1794427	$C_{16}H_{18}O_9$	C1C(C(C(CC1(C(=O)O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O	
3	Caffeic acid	Phenol	CID 689043	$C_9H_8O_4$	C1=CC(=C(C=C1C=CC(=O)O)O)O	
4	Rutin	Flavonoid	CID 5280805	$C_{27}H_{30}O_{16}$	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O	
5	Quercetin	Flavonoid	CID 5280343	$C_{15}H_{10}O_7$	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O	
6	Kaempferol	Flavonoid	CID 5280863	$C_{15}H_{10}O_6$	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O	

plant is *Senecio biafrae* leaf as reported by Ajiboye et al. [5]. *Senecio biafrae* (local name Worowo in Yoruba speaking part of Nigeria) belongs to the group of vegetables that grow in large quantities as undercover in tree crop plantation. This leafy vegetable is also considered for its high medicinal value as the juice extracted from the leaf is wholly applied to fresh wounds or cuts as a styptic in the rural community for man and animal use [15]. It is one of the major green leafy vegetables consumed in Nigeria, Ghana, Benin, Sierra Leone, Cameroon and Gabon [5]. This plant leaf is endowed with medicinal properties [3]. Ajiboye et al. [4] documented the phytochemical constituents of the plant's leaf, with a high content of phenolic compounds. Because of this, in silico prediction of druggable phytochemicals from this plant leaf against α-amylase and α-glucosidases may be a breakthrough in designing a new drug in the management of diabetes mellitus.

Methods

Retrieval of bioactive compounds

Six bioactive compounds were gotten from a published article by Ajiboye et al. [5], and their chemical structures were reclaimed from PubChem (https://pubchem.ncbi.nlm.nih.gov/) database in SDF format, which was then

Table 2 Analysis of oral drug-likeness of the six bioactive compounds using Lipinski's rule of five

Bioactive Compounds	Molecular weight (g/mol)	Log P	Number of hydrogen bond donor	Number of hydrogen bond acceptor	Molar refractivity
Caffeic acid	180.16	0.97	3	4	47.16
Gallic acid	170.12	0.21	4	5	38.47
Metformin	129.16	0.34	3	2	36.93
Quercetin	302.24	1.63	5	7	78.04
Rutin	617.66	− 92.39	10	14	147.66
Chlorogenic acid	354.31	0.87	6	9	83.50
Kaempferol	286.24	1.70	4	6	76.01

Table 3 ADMET distribution profiles of the six bioactive compounds

Bioactive compounds	G1 Absorption	BBB Permeability	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
Caffeic acid	High	No	No	No	No	No	No	No
Gallic acid	High	No	No	No	No	No	No	Yes
Metformin	High	No	No	No	No	No	No	No
Quercetin	High	No	No	Yes	No	No	Yes	Yes
Rutin	Low	No	Yes	No	No	No	No	No
Chlorogenic acid	Low	No	No	No	No	No	No	No
Kaempferol	High	No	No	Yes	No	No	Yes	Yes

converted into PDB format with the aid of Open Babel Converter (http://openbabel.org/wiki/Main_Page) [21].

Examining the bioactive compounds for Lipinski's rule of five

This rule assesses the drug-likeness of the six bioactive compounds using molinspiration cheminformatics tool. This includes the molecular weight of the bioactive compounds, Log P, number of hydrogen bond donors, number of hydrogen bond receptors, and molecular refractivity [17].

ADMET prediction

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) were analyzed [18]. The study includes mutagenicity, toxicological dosage level as well as pharmacologically properties of each bioactive compounds, which were done using Swissadme (http://www.swissadme.ch) and admetSAR servers [11].

Molecular docking

The docking analyses of the six bioactive compounds and metformin (standard antidiabetic drug) with α-amylase and α-glucosidase were determined using AutoDockVina. The best complexes showing the highest score of molecular interactions between each ligand (bioactive compounds) with α-amylase and α-glucosidase enzymes used as receptors were selected. Also, PyMOL was used to view the amino acids of α-amylase and α-glucosidase interacting with the inhibitors at active sites.

Results

Selection of bioactive compounds

The six bioactive compounds obtained from *Senecio biafrae* leaf used in this study, belong to two chemical classes (phenol and flavonoid) as indicated in Table 1.

Analysis of Lipinski's rule of five

In fulfilling the drug-likeness, molecules that have a molecular mass not greater than 500 Da, LogP not greater than 5, hydrogen bond donor not greater than 5, hydrogen bond acceptor not greater than 10, and molar refractivity between 40 to 130. As illustrated in Table 2 only caffeic acid, quercetin and kaempferol obey this rule. Gallic acid, metformin, and chlorogenic acid slightly meet the criteria of this rule. Gallic acid and metformin have molar refractivity lower than 40 while chlorogenic acid has a number of hydrogen bonds above 5. On the other hand, rutin did not meet four of the Lipinski's rule of five.

ADMET profiles

As depicted in Table 3, all the bioactive compounds used in this study, as well as metformin, have high gastrointestinal tract (GIT) absorption except rutin and chlorogenic acid with low GIT absorption. All the six

Table 4 AutoDockVina results for each bioactive compound with their binding affinity against α-amylase and α-glucosidase

S/No	Bioactive Compounds	Binding affinity (Kcal/mol) against α-amylase	Binding affinity (Kcal/mol) against α-glucosidase
1	Caffeic acid	−6.5	− 6.5
2	Chlorogenic acid	−7.2	− 8.3
3	Gallic acid	− 5.4	−6.1
4	Kaempferol	−8.1	− 8.5
5	Quercetin	−8.2	−8.4
6	Rutin	−8.2	−8.5
7	Metformin	−4.5	−5.2

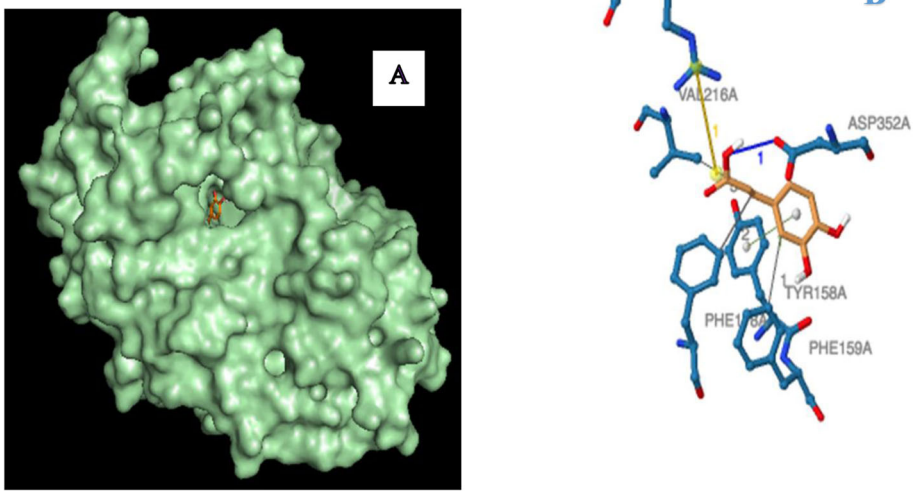


Fig. 1 Binding pose and binding site of caffeic acid with α-glucosidase (panel A), molecular interaction of caffeic acid with amino acid residues within the binding pocket of the protein structure (panel B)

bioactive compounds have no blood-brain barrier permeability, and only rutin can serve as the P-glycoprotein (P-gp) substrate. In another vein, all the six bioactive compounds and metformin (the standard used) are non-inhibitors of cytochrome P450 isoforms, except quercetin which inhibits CYP1A2, CYP2D6, and CYP3A4; gallic acid inhibits CYP3A4; and kaempferol inhibits CYP1A2, CYP2D6, and CYP3A4.

Molecular docking and binding energy analysis

The binding activity of α-amylase and α-glucosidase are shown in Table 4 with all the six bioactive compounds having a higher binding affinity than the standard drug used. In α-amylase, rutin and quercetin have the highest binding affinity of −8.2 kcal/mol while in α-glucosidase, rutin and kaempferol have the highest binding affinity of − 8.5 kcal/mol. Figures 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 shows the binding pose of each ligand with their receptors as well as their molecular interactions with different amino acid residues within the binding pocket of the protein structure. All the ligands form hydrophobic interaction, hydrogen bond, and π stacking with both of α-amylase and α-glucosidase using different amino acids (Tables 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18).

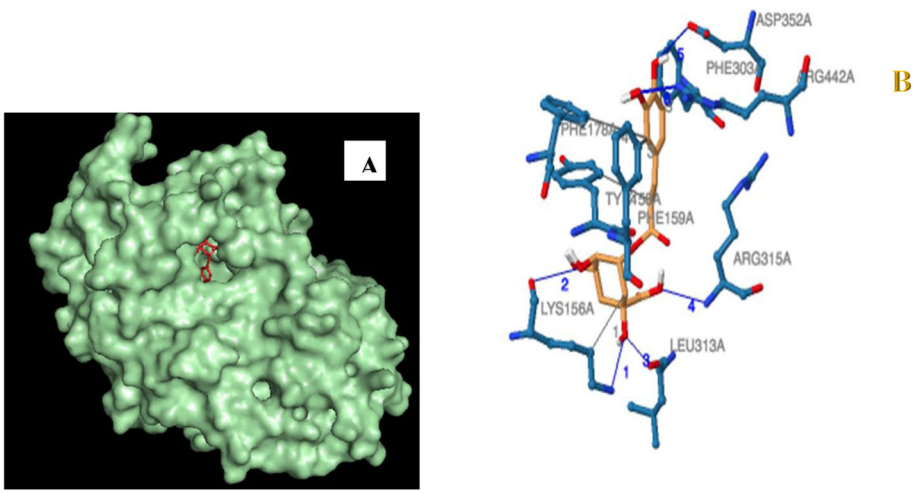


Fig. 2 Binding pose and binding site of chlorogenic acid with α-glucosidase (panel A), molecular interaction of chlorogenic acid with amino acid residues within the binding pocket of the protein structure (panel B)

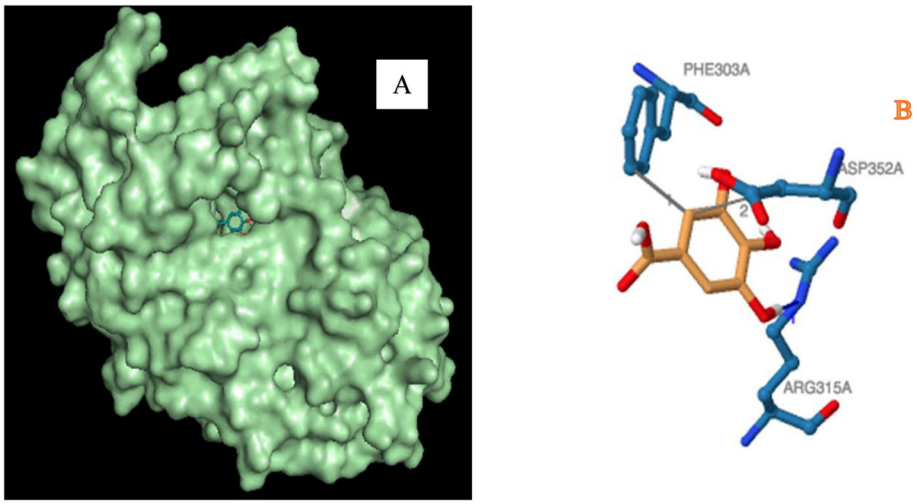


Fig. 3 Binding pose and binding site of gallic acid with α-glucosidase (panel A), molecular interaction of gallic acid with amino acid residues within the binding pocket of the protein structure (panel B)

Discussion

The present study was designed to investigate the in silico molecular interaction of bioactive compounds from *Senecio biafrae* with key enzymes related to diabetes mellitus. Diabetes mellitus (DM) is a metabolic disorder with increasing prevalence all over the world. According to Li and Ding [16], there were approximately 366 million people suffered from DM (aged 20–79 years) in 2011 and this figure would climb up to 552 million by the year 2030. DM is characterized by hyperglycemia as well as the development of diabetes-specific complications. These complications can result in disastrous consequences, but many synthetic drugs used today failed to complete long-term glycemic control [22]. Clinically, novel treatments with fewer side effects are desirable for the control of DM as well as its complications.

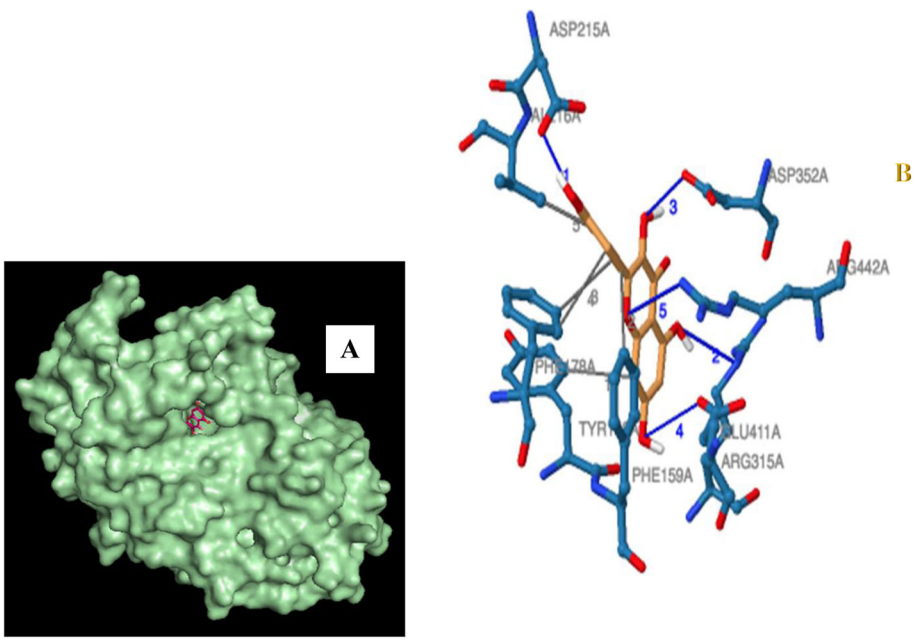


Fig. 4 Binding pose and binding site of kaempferol with α-glucosidase (panel A), molecular interaction of kaempferol with amino acid residues within the binding pocket of the protein structure (panel B)

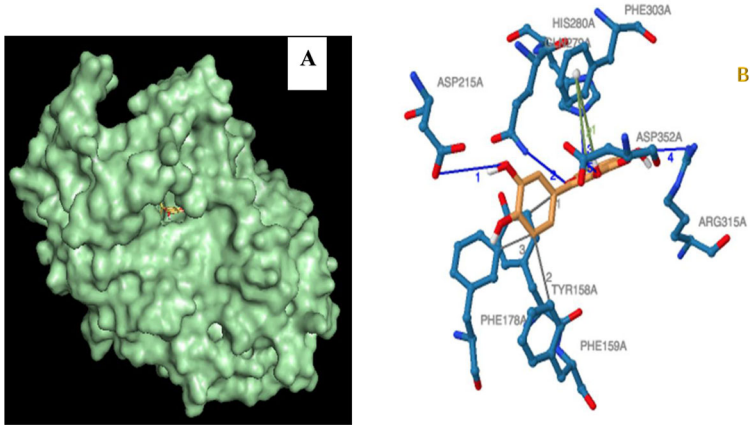


Fig. 5 Binding pose and binding site of quercetin with α-glucosidase (panel A), molecular interaction of quercetin with amino acid residues within the binding pocket of the protein structure (panel B)

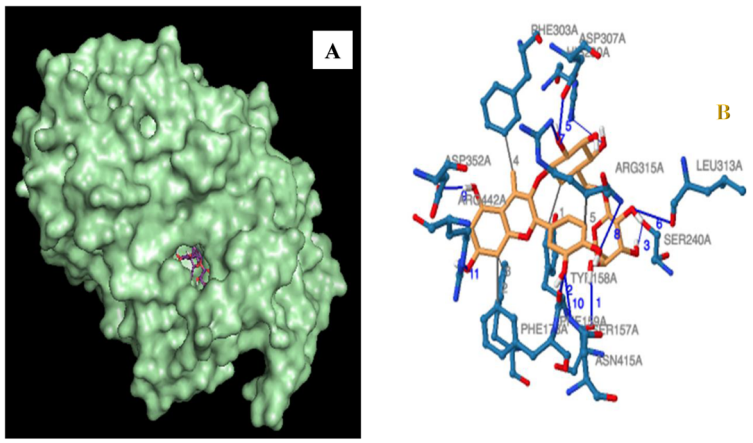


Fig. 6 Binding pose and binding site of rutin with α -glucosidase (panel A), molecular interaction of rutin with amino acid residues within the binding pocket of the protein structure (panel B)

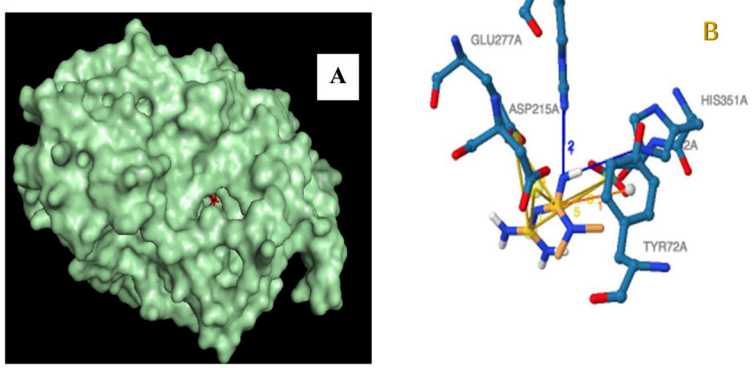


Fig. 7 Binding pose and binding site of metformin with α-glucosidase (panel A), molecular interaction of metformin with amino acid residues within the binding pocket of the protein structure (panel B)

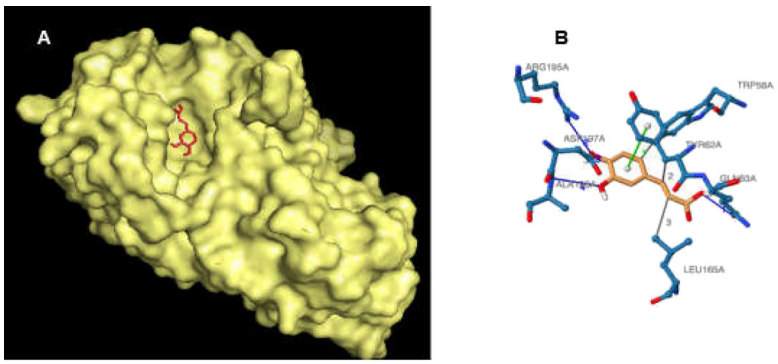


Fig. 8 Binding pose and binding site of caffeic acid with alpha amylase (panel A), molecular interaction of caffeic acid with amino acid residues within the binding pocket of the protein structure (panel B)

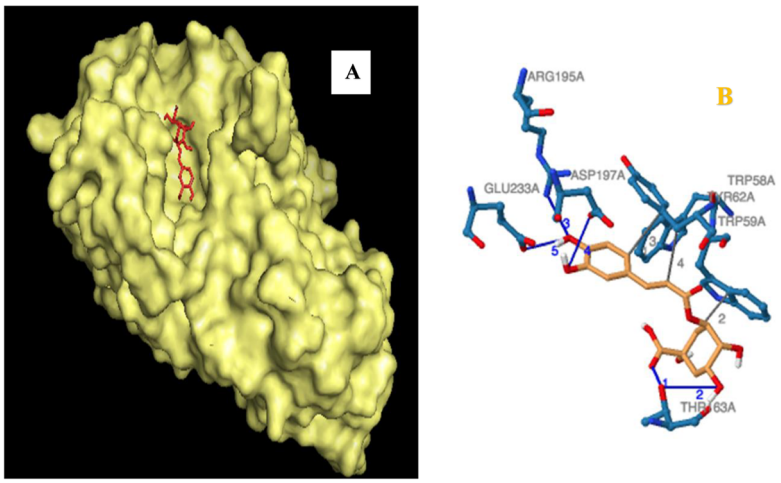


Fig. 9 Binding pose and binding site of chlorogenic acid with α- amylase (panel A), molecular interaction of chlorogenic acid with amino acid residues within the binding pocket of the protein structure (panel B)

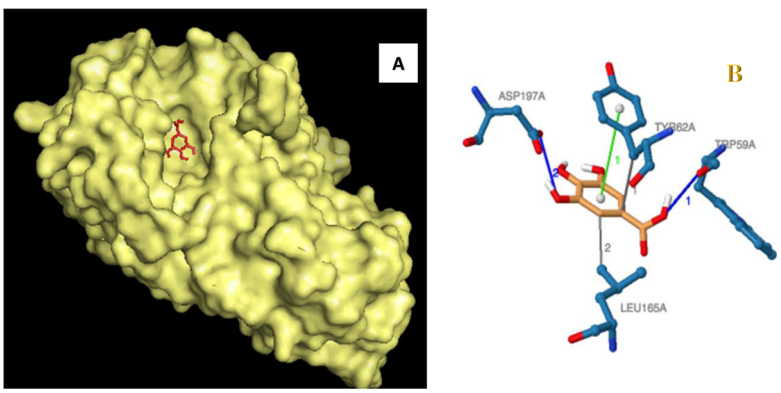


Fig. 10 Binding pose and binding site of gallic acid with α-amylase (panel A), molecular interaction of gallic acid with amino acid residues within the binding pocket of the protein structure (panel B)

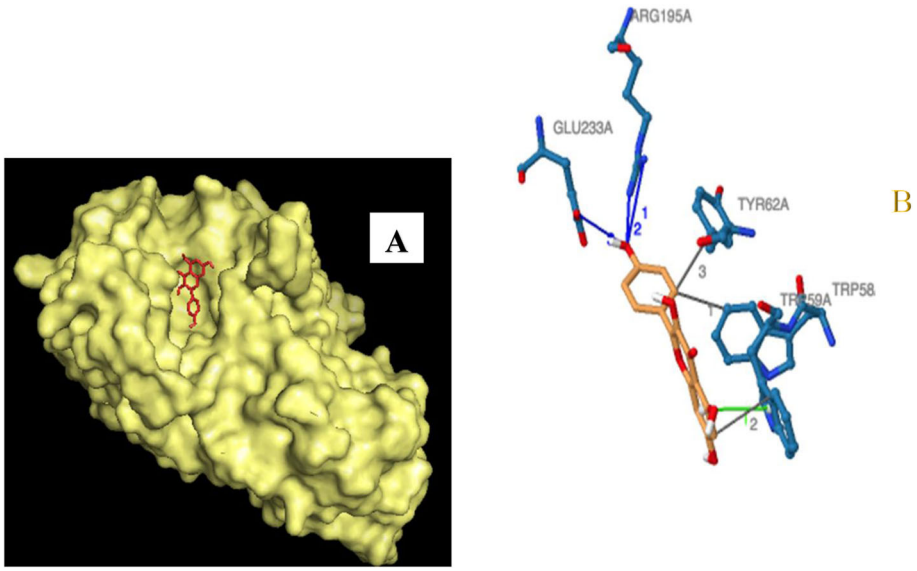


Fig. 11 Binding pose and binding site of kaempferol with α-amylase (panel A), molecular interaction of kaempferol with amino acid residues within the binding pocket of the protein structure (panel B)

Interestingly, the use of plant extracts that possess widespread biological functions has increased in recent years [16, 22].

According to Oboh [19], the phenolic constituent of plants endowed with antioxidants capable of scavenging free radicals produced in the body. The presence of flavonoids and phenolics (gallic acid, chlorogenic, caffeic acid, rutin, quercetin, and kaempferol) in *Senecio biafrae* may also contribute to lowering cellular oxidative stress and inhibit α-amylase, and α-glucosidase activities among others [1]. The uses of the phenolic extract of *S. biafrae* leaf in vitro in the management of type II diabetes mellitus are scanty in the literature.

Alpha-glucosidase is a glucosidase located in the brush border of the small intestine that acts upon α $(1 \rightarrow 4)$ bonds [8]. Alpha-glucosidase breaks down starch and disaccharides to glucose. Alpha-glucosidase inhibitor competitively and reversibly inhibits alpha-glucosidase in the intestines. This inhibition lowers the rate of glucose absorption through delayed carbohydrate digestion and extended digestion time [23]. Hence, alpha-glucosidase as well as alpha-amylase (found in the salivary gland) inhibitors are used as anti-diabetic drugs in combination with other anti-diabetic drugs.

As demonstrated in Table 2, caffeic acid, quercetin, and kaempferol obey Lipinski's rule of five or Pfizer's

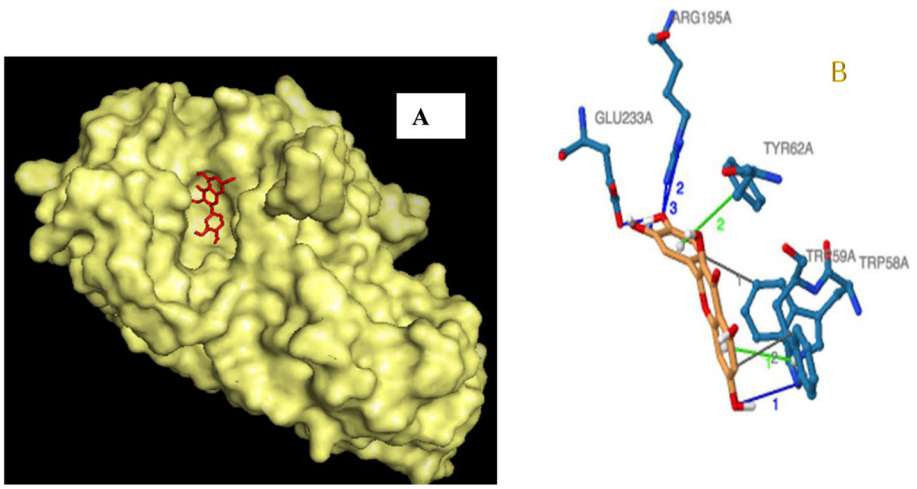


Fig. 12 Binding pose and binding site of quercetin with α-amylase (panel A), molecular interaction of quercetin with amino acid residues within the binding pocket of the protein structure (panel B)

Table 5 Hydrogen bonding and hydrophobic interactions between caffeic acid and amino acid residues within α-glucosidase binding site

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	159A	PHE	3.96	4838	1296
2	178A	PHE	3.61	4843	1459
3	216A	VAL	3.93	4843	1769

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	352A	ASP	2.31	3.15	143.42	✗	✓	4847 [O.co2]	2885 [O.co2]

π-Stacking

Index	Residue	AA	Distance	Angle	Offset	Type	Ligand Atoms
1	158A	TYR	4.88	69.65	0.81	T	4837, 4838, 4839, 4840, 4841, 4842

Salt Bridges

Index	Residue	AA	Distance	Protein positive?	Ligand Group	Ligand Atoms
1	213A	ARG	5.27	✓	Carboxylate	4846, 4847

rule, which is one of the techniques normally employed in assessing the drug-likeness of a chemical compound. This rule gives a clue if a chemical compound possesses pharmacological properties that may be plausible as an oral drug for humans or not [17, 21]. This implies that caffeic acid, quercetin, and kaempferol may serve as potential drugs in the management of diabetes mellitus and probably better than metformin.

Caffeic acid, gallic acid, quercetin, and kaempferol have high absorption in the human gastrointestinal tract (Table 3). This means that these bioactive compounds can be easily metabolized in the human body system. Also, according to Daneman and Prat [9], the blood-brain barrier (BBB) is a selective semipermeable border of endothelial cells that inhibits solutes in the circulating blood from crossing into the extracellular fluid of the central nervous system where neurons reside. The blood-brain barrier is formed by endothelial cells and permits the passage of some molecules by passive diffusion and selective transport of different nutrients, ions,

Table 6 Hydrogen bonding and hydrophobic interactions between chlorogenic acid and amino acid residues within α -glucosidase binding site

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	156A	LYS	3.78	4839	1267
2	158A	TYR	3.56	4846	1283
3	159A	PHE	3.73	4849	1296
4	178A	PHE	3.98	4849	1459
5	303A	PHE	3.98	4852	2474

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	156A	LYS	2.43	3.18	129.09	✓	✓	1269 [N3+]	4860 [O3]
2	156A	LYS	3.12	3.50	104.58	✗	✗	4858 [O3]	1264 [O2]
3	313A	LEU	2.55	2.93	102.73	✗	✗	4860 [O3]	2541 [O2]
4	315A	ARG	2.20	3.08	147.49	✓	✗	2557 [Nam]	4864 [O.co2]
5	352A	ASP	2.18	2.96	135.27	✗	✓	4856 [O3]	2885 [O.co2]
6	442A	ARG	2.51	3.00	110.44	✓	✓	3612 [Ng+]	4854 [O3]

Table 7 Hydrogen bonding and hydrophobic interactions between gallic acid and amino acid residues within α-glucosidase binding site

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	303A	PHE	3.49	4842	2474
2	352A	ASP	3.76	4842	2882

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	315A	ARG	2.79	3.75	168.90	✘	✔	4847 [O3]	2564 [Ng+]

organic anions, and macromolecules (like glucose, water, and amino acids) that are key to neural function as documented by Gupta et al. [14]. The no blood-brain barrier permeability of caffeic acid, gallic acid, quercetin, rutin, chlorogenic acid, kaempferol, and metformin support their non- mutagens and non-carcinogens potentials (Table 3).

Caffeic acid, gallic acid, quercetin, chlorogenic acid, kaempferol, and metformin are non-substrate and non-inhibitor of P-glycoprotein (P-gp). Hence, these compounds cannot be acknowledged by the P-gp for any efflux [11]. P-gp is a plasma membrane protein that acts as a localized drug transport mechanism, that energetically distributing drugs out of the cell, therefore they are important proteins involved in xenobiotic efflux. It was only rutin that has the ability as a substrate of P-gp, which implies that P-gp can identify this compound and probably cause its efflux (Table 3). Furthermore, Nisha et al. [18] reported that cytochrome P450 (CYP P450) is a member of microsomal enzymes involved in the metabolism of drugs in the human body system. In this study, the CYP 450 inhibitory profiles were evaluated using CYP1A2, CYP 2C19, CYP 2C9, CYP 2D6 and CYP 3A4. Hence, caffeic acid, metformin (the standard used), rutin and chlorogenic acid demonstrated no inhibitory potential with the possibility of a lower drug-interaction (Table 3).

Rutin and kaempferol (– 8.5 kcal/mol), followed by quercetin (– 8.4 kcal/mol), ranked highest in binding affinity with alpha-glucosidase better than that of a standard drug, metformin (– 5.2 kcal/mol) (Table 4). The

Table 8 Hydrogen bonding and hydrophobic interactions between kaemferol and amino acid residues within α-glucosidase binding site

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	158A	TYR	3.45	4845	1283
2	159A	PHE	3.62	4853	1298
3	178A	PHE	3.42	4848	1459
4	178A	PHE	3.72	4852	1457
5	216A	VAL	3.22	4849	1769

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	215A	ASP	1.93	2.90	171.25	✘	✔	4854 [O3]	1763 [O.co2]
2	315A	ARG	2.52	3.40	148.89	✘	✔	4858 [O3]	2564 [Ng+]
3	352A	ASP	2.35	2.70	100.23	✘	✔	4856 [O3]	2885 [O.co2]
4	411A	GLU	3.28	3.79	113.91	✘	✔	4860 [O3]	3358 [O.co2]
5	442A	ARG	3.75	4.09	103.85	✔	✔	3612 [Ng+]	4837 [O2]

Table 9 Hydrogen bonding and hydrophobic interactions between quercetin and amino acid residues within α-glucosidase binding site

Hydrophobic Interactions ----

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	158A	TYR	3.54	4845	1285
2	159A	PHE	3.51	4852	1296
3	178A	PHE	3.15	4852	1459

Hydrogen Bonds ——

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	215A	ASP	3.24	4.07	143.41	✗	✓	4854 [O3]	1763 [O.co2]
2	279A	GLN	2.78	3.37	119.17	✓	✓	2275 [Nam]	4837 [O2]
3	280A	HIS	2.06	2.99	158.19	✗	✓	4862 [O3]	2285 [N2]
4	315A	ARG	2.70	3.04	100.64	✓	✓	2566 [Ng+]	4860 [O3]
5	352A	ASP	2.97	3.64	127.35	✗	✓	4858 [O3]	2885 [O.co2]

π-Stacking ---- ----

Index	Residue	AA	Distance	Angle	Offset	Type	Ligand Atoms
1	303A	PHE	5.23	63.38	1.94	T	4839, 4840, 4844, 4845, 4846, 4847
2	303A	PHE	4.97	63.11	1.08	T	4837, 4839, 4840, 4841, 4842, 4843

interactions of these compounds were stabilized by hydrogen bonding and hydrophobic interaction. During the docking simulation of alpha-glucosidase with the selected bioactive compounds from *Senecio biafrae*, eleven residues within the active site of alpha-glucosidase (Ser157, Tyr158, Ser240, His280, Asp307, Lue313, Arg315, Asp352, Asn415, Arg442) were intricate in hydrogen bond formation with rutin, five residues within the active site of alpha-glucosidase (Asp215, Arg315, Asp352, Glu411, Arg442) were saliently involved in hydrogen bond formation with kaemferol while amino acids (Asp215, Gln279, His280, Arg315, Asp352) were important in hydrogen bond formation with quercetin (Figs. 1, 2, 3, 4, 5, 6 and 7). Hydrophobic interactions

Table 10 Hydrogen bonding and hydrophobic interactions between rutin and amino acid residues within α-glucosidase binding site

Hydrophobic Interactions ----

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	158A	TYR	3.87	4838	1285
2	159A	PHE	3.21	4852	1296
3	178A	PHE	3.19	4852	1459
4	303A	PHE	2.53	4847	2474
5	315A	ARG	3.69	4863	2561

Hydrogen Bonds ——

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	157A	SER	2.78	3.66	148.98	✗	✗	4880 [O3]	1273 [O2]
2	158A	TYR	2.64	3.24	119.47	✗	✗	4865 [O3]	1279 [O2]
3	240A	SER	2.91	3.83	156.28	✗	✓	4882 [O3]	1949 [O3]
4	280A	HIS	2.83	3.23	105.52	✗	✓	4888 [O3]	2285 [N2]
5	307A	ASP	1.90	2.54	120.59	✗	✓	4869 [O3]	2505 [O.co2]
6	313A	LEU	3.17	3.97	139.42	✗	✗	4884 [O3]	2541 [O2]
7	315A	ARG	2.64	3.19	115.77	✓	✓	2566 [Ng+]	4869 [O3]
8	315A	ARG	2.55	3.41	145.83	✓	✗	2557 [Nam]	4867 [O3]
9	352A	ASP	1.93	2.81	148.30	✗	✓	4855 [O3]	2885 [O.co2]
10	415A	ASN	2.06	2.87	137.79	✓	✓	3393 [Nam]	4865 [O3]
11	442A	ARG	2.07	2.91	142.18	✓	✓	3612 [Ng+]	4857 [O3]

Table 11 Hydrogen bonding and hydrophobic interactions between metformin and amino acid residues within α- glucosidase binding site

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	213A	ARG	3.28	4.05	136.97	✓	✓	1746 [Ng+]	4839 [Ng+]
2	213A	ARG	2.41	3.39	175.25	✓	✓	1747 [Ng+]	4839 [Ng+]
3	351A	HIS	3.29	4.04	138.86	✗	✓	4839 [Ng+]	2877 [N2]

π-Cation Interactions

Index	Residue	AA	Distance	Offset	Protein charged?	Ligand Group	Ligand Atoms
1	72A	TYR	5.11	1.18	✗	guanidine	4837, 4838, 4839

Salt Bridges

Index	Residue	AA	Distance	Protein positive?	Ligand Group	Ligand Atoms
1	215A	ASP	5.49	✗	Guanidine	4838, 4840, 4841
2	215A	ASP	3.79	✗	Guanidine	4837, 4838, 4839
3	277A	GLU	4.22	✗	Guanidine	4838, 4840, 4841
4	277A	GLU	3.53	✗	Guanidine	4837, 4838, 4839
5	352A	ASP	4.73	✗	Guanidine	4838, 4840, 4841
6	352A	ASP	3.85	✗	Guanidine	4837, 4838, 4839

also contributed to the interaction of rutin with amino acid residues (Tyr158, Phe159, Phe178, Phe303, Arg315), kaempferol with amino acid residues (Tyr158, Phe159, Phe178, Val216) and quercetin with amino acid residue (Tyr158, Phe159, Phe178) within the active site of alpha-glucosidase (Tables 5, 6, 7, 8, 9, 10 and 11). Therefore, inhibition of alpha-glucosidase by rutin, kaempferol, and quercetin is a potent target for effective anti-diabetes drug design as it effectively checkmates the level of blood glucose.

Alpha-amylase is an enzyme that hydrolyzes alpha bonds of large, alpha-linked polysaccharides, such as starch and glycogen, yielding glucose and maltose that hydrolyzes alpha bonds of large, alpha-linked polysaccharides, such as starch and glycogen, yielding glucose and maltose (Gaspar et al., [13]). It is the major form of amylase found in humans and other mammals. Alpha -amylases are enzymes that hydrolyze starch molecules to give diverse products including dextrins and progressively smaller polymers composed of glucose units

Table 12 Hydrogen bonding and hydrophobic interactions between caffeic acid and amino acid residues within α-amylase binding site

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	58A	TRP	3.58	3942	470
2	62A	TYR	3.65	3946	510
3	165A	LEU	3.84	3947	1300

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	63A	GLN	2.43	3.14	129.13	✗	✓	3950 [O.co2]	525 [O2]
2	195A	ARG	2.35	3.33	174.80	✓	✓	1543 [Ng+]	3954 [O3]
3	197A	ASP	2.18	2.82	121.77	✗	✓	3954 [O3]	1558 [O.co2]
4	198A	ALA	3.69	4.02	102.44	✓	✗	1560 [Nam]	3952 [O3]

π-Stacking

Index	Residue	AA	Distance	Angle	Offset	Type	Ligand Atoms
1	62A	TYR	4.38	17.00	1.44	P	3940, 3941, 3942, 3943, 3944, 3945

Table 13 Hydrogen bonding and hydrophobic interactions between chlorogenic acid and amino acid residues within α-amylase binding site

Hydrophobic Interactions ····

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	58A	TRP	3.80	3956	470
2	59A	TRP	3.72	3942	479
3	62A	TYR	3.67	3956	511
4	62A	TYR	3.46	3949	510

Hydrogen Bonds —

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	163A	THR	2.06	3.02	173.06	✔	✔	1288 [O3]	3966 [O.co2]
2	163A	THR	3.25	3.87	122.53	✖	✔	3969 [O3]	1288 [O3]
3	195A	ARG	2.21	3.01	137.87	✔	✔	1543 [Ng+]	3959 [O3]
4	197A	ASP	2.98	3.73	134.26	✖	✔	3957 [O3]	1558 [O.co2]
5	233A	GLU	2.09	3.00	154.46	✖	✔	3959 [O3]	1853 [O-]

Table 14 Hydrogen bonding and hydrophobic interactions between gallic acid and amino acid residues within α -amylase binding site

Hydrophobic Interactions ····

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	62A	TYR	3.50	3940	510
2	165A	LEU	3.61	3945	1300

Hydrogen Bonds —

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	59A	TRP	2.16	2.90	130.41	✖	✖	3948 [O.co2]	475 [O2]
2	197A	ASP	2.61	3.53	156.25	✖	✔	3952 [O3]	1558 [O.co2]

π-Stacking ···· ····

Index	Residue	AA	Distance	Angle	Offset	Type	Ligand Atoms
1	62A	TYR	4.72	19.44	1.96	P	3940, 3941, 3942, 3943, 3944, 3945

Table 15 Hydrogen bonding and hydrophobic interactions between kaempferol and amino acid residues within α -amylase binding site

Hydrophobic Interactions ····

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	58A	TRP	3.70	3956	470
2	59A	TRP	3.76	3950	482
3	62A	TYR	3.58	3956	511

Hydrogen Bonds —

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	195A	ARG	3.38	4.07	128.81	✔	✔	1542 [Ng+]	3957 [O3]
2	195A	ARG	2.14	3.12	168.68	✔	✔	1543 [Ng+]	3957 [O3]
3	233A	GLU	2.40	3.21	138.87	✖	✔	3957 [O3]	1852 [O3]

π-Stacking ···· ····

Index	Residue	AA	Distance	Angle	Offset	Type	Ligand Atoms
1	59A	TRP	3.91	3.11	1.49	P	3942, 3943, 3947, 3948, 3949, 3950

Table 16 Hydrogen bonding and hydrophobic interactions between quercetin and amino acid residues within α-amylase binding site

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	58A	TRP	3.66	3956	470
2	59A	TRP	3.75	3950	482

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	59A	TRP	2.77	3.69	157.40	✗	✓	3965 [O3]	480 [N2]
2	195A	ARG	3.15	3.82	127.21	✓	✓	1542 [Ng+]	3959 [O3]
3	195A	ARG	1.91	2.89	170.36	✓	✓	1543 [Ng+]	3959 [O3]
4	233A	GLU	2.22	3.02	137.88	✗	✓	3959 [O3]	1853 [O-]

π-Stacking

Index	Residue	AA	Distance	Angle	Offset	Type	Ligand Atoms
1	59A	TRP	4.01	3.95	1.68	P	3942, 3943, 3947, 3948, 3949, 3950
2	62A	TYR	4.60	25.41	1.73	P	3951, 3952, 3953, 3954, 3955, 3956

Table 17 Hydrogen bonding and hydrophobic interactions between rutin and amino acid residues within α-amylase binding site

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	59A	TRP	3.78	3950	477
2	162A	LEU	3.88	3966	1282
3	165A	LEU	3.60	3955	1300
4	235A	ILE	3.50	3980	1868

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	63A	GLN	3.25	3.83	119.16	✗	✓	3960 [O3]	525 [O2]
2	151A	TYR	3.58	4.08	115.97	✓	✓	1194 [O3]	3975 [O3]
3	197A	ASP	3.04	3.59	116.13	✗	✓	3968 [O3]	1558 [O.co2]
4	300A	ASP	2.32	2.73	103.63	✗	✓	3972 [O3]	2388 [O-]

Table 18 Hydrogen bonding and hydrophobic interactions between metformin and amino acid residues within α-amylase binding site

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Sidechain	Donor Atom	Acceptor Atom
1	101A	HIS	2.83	3.36	114.41	✗	✓	3942 [Ng+]	830 [N2]
2	198A	ALA	3.57	3.95	105.86	✓	✗	1560 [Nam]	3943 [Ng+]

Salt Bridges

Index	Residue	AA	Distance	Protein positive?	Ligand Group	Ligand Atoms
1	197A	ASP	4.36	✗	Guanidine	3941, 3943, 3944
2	197A	ASP	3.64	✗	Guanidine	3940, 3941, 3942
3	233A	GLU	3.38	✗	Guanidine	3941, 3943, 3944
4	233A	GLU	5.22	✗	Guanidine	3940, 3941, 3942

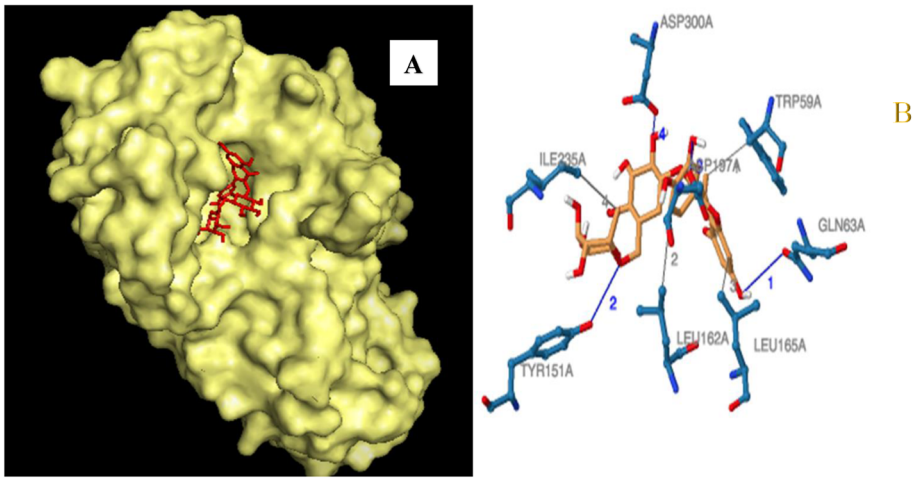


Fig. 13 Binding pose and binding site of rutin with α-amylase (panel A), molecular interaction of rutin with amino acid residues within the binding pocket of the protein structure (panel B)

which causes hyperglycemia and development of type II diabetes mellitus [2]. Rutin (– 8.2 kcal/mol), quercetin (– 8.2 kcal/mol) and kaempferol (– 8.1 kcal/mol) exhibited better interaction by showing more binding affinity with alpha-amylase than the standard drug metformin (– 4.5 kcal/mol) (Table 4) and this interaction was stabilized and sustained by hydrophobic interaction and hydrogen bonding. Gln63, Tyr151, Asp197, Asp300 are important residues for hydrogen bonding when rutin interacted with α-amylase. While Trp59, Arg195, Glu233 were very germane for the formation of hydrogen bonding when quercetin interacted with α-amylase, Arg195 and Glu233 were also very important residues for hydrogen bonding when kaempferol interacted with α-amylase (Figs. 8, 9, 10, 11, 12, 13 and 14). Residues (Trp59, Lue162, Lue165, Ile235), (Trp58, Trp59) and (Trp58, Trp59, Tyr62), were responsible for hydrophobic interaction when α-

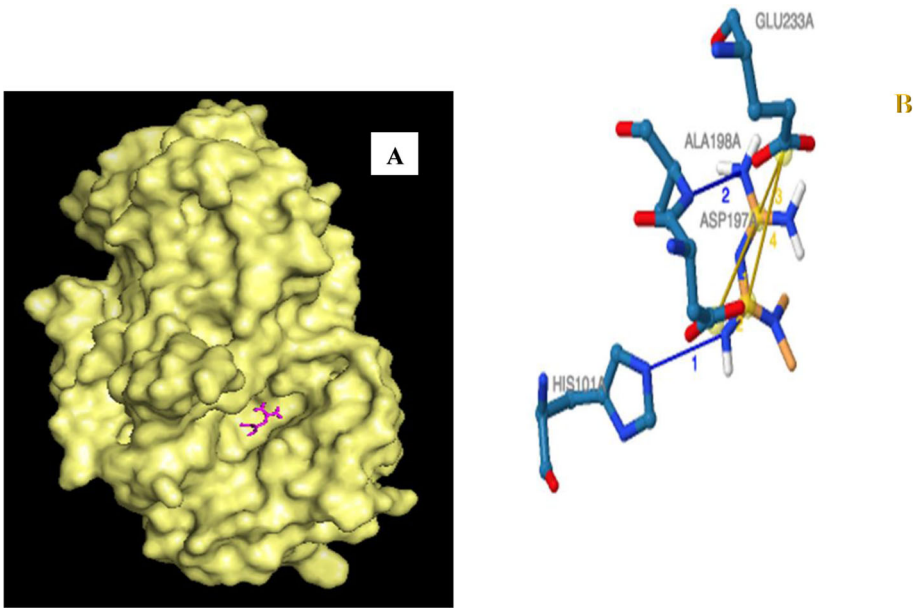


Fig. 14 Binding pose and binding site of metformin with α-amylase (panel A), molecular interaction of metformin with amino acid residues within the binding pocket of the protein structure (panel B)

amylase interacted with rutin, quercetin, and kaempferol respectively (Table 12, 13, 14, 15, 16, 17 and 18). Hence, the inhibition of alpha-amylase by rutin, quercetin, and kaemferol is implicative of their vast anti-diabetic abilities and thus, a potent alternative for synthetic drugs.

Conclusion

From the results obtained in this study, it can be deduced that the bioactive compounds used especially caffeic acid was the only compound that obeys Lipinski's rule of five, good ADMET results, although ranked 4th in binding affinity against α-glucosidase and 5th in binding affinity against α-amylase may be a promising therapeutic agent than the metformin in the management of type II diabetes mellitus. In another word, compounds that can also be applicable as a potent alternative drug in the management of type II diabetes mellitus are quercetin and kaempferol, they obey Lipinski's rule of five, slightly poor ADMET results and they have high binding affinity against both alpha-glucosidase and alpha-amylase while rutin only has good binding affinity but does not obey Lipinski's rule of five and slightly bad ADMET profiles.

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Author's contributions
This is a single-author manuscript, so everything about this manuscript was done by BOA. The author read and approved the final manuscript.

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Declarations

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Competing interests
The authors declare that they have no competing interests.

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